THERAPEUTIC IMPLICATIONS FOR PREGNANT WOMEN WITH SYSTEMIC AUTOIMMUNE DISEASES AND THEIR CHILDREN

EDITED BY: Cecilia Beatrice Chighizola, Maria Gerosa, Guilherme Ramires De Jesús and Tadej Avcin

PUBLISHED IN: Frontiers in Pharmacology and Frontiers in Pediatrics

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88974-073-4
DOI 10.3389/978-2-88974-073-4

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

THERAPEUTIC IMPLICATIONS FOR PREGNANT WOMEN WITH SYSTEMIC AUTOIMMUNE DISEASES AND THEIR CHILDREN

Topic Editors:
Cecilia Beatrice Chighizola, University of Milan, Italy
Maria Gerosa, University of Milan, Italy
Guilherme Ramires De Jesús, Rio de Janeiro State University, Brazil
Tadej Avcin, University Medical Centre Ljubljana, Slovenia

Citation: Chighizola, C. B., Gerosa, M., De Jesús, G. R., Avcin, T., eds. (2022). Therapeutic Implications for Pregnant Women With Systemic Autoimmune Diseases and Their Children. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-88974-073-4

Table of Contents

frontiers in Pharmacology

EDITORIAL
published: 26 November 2021
doi: 10.3389/fphar.2021.773970

Editorial: Therapeutic Implications for Pregnant Women With Systemic Autoimmune Diseases and Their Children

Cecilia Beatrice Chighizola[1,2]*, *Guilherme Ramires de Jesús*[3,4], *Maria Gerosa*[1,5] and *Tadej Avčin*[6,7]

[1]Department of Clinical Sciences and Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, University of Milan, Milan, Italy, [2]Pediatric Rheumatology Unit, ASST G. Pini & CTO, Milan, Italy, [3]Department of Obstetrics, Instituto Fernandes Figueira, FIOCRUZ, Rio de Janeiro, Brazil, [4]Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil, [5]Clinical Rheumatology Unit, ASST G. Pini & CTO, Milan, Italy, [6]Department of Allergology, Rheumatology and Clinical Immunology, Children's Hospital, Ljubljana, Slovenia, [7]University Medical Centre Ljubljana, University of Ljubljana, Ljubljana, Slovenia

Keywords: pregnancy, rheumatic diseases, treatment, obstetric complications, disease activity, offspring

Editorial on the Research Topic

Therapeutic Implications for Pregnant Women With Systemic Autoimmune Diseases and Their Children

The close interplay between systemic autoimmune diseases and reproductive health has long been known: gestations in women with rheumatic disease are at higher risk of maternal and fetal complications. In addition, the physiologic hormonal changes that characterize the different phases of pregnancy modulate disease activity, in some diseases exacerbating the disease activity, while in others improving the disease severity. The impact of disease activity on reproductive issues in rheumatology is crucial: in many different conditions, disease activity before and during pregnancy is the main predictor of gestational outcome. This observation implies the compelling relevance of tight disease control throughout gestational course, which in turn translates into the necessity to ameliorate the pharmacological approach to rheumatic pregnant patients.

If the impact of rheumatologic conditions on pregnancy progression had been ascertained in the early days, the scientific community could not yet reach a unanimous consensus whether rheumatic conditions can affect female fertility. As a matter of fact, women with rheumatoid arthritis (RA), the most common rheumatologic inflammatory disease, take a longer time to conceive and have decreased family size compared to healthy controls. Again, active disease is the main determinant of these difficulties in achieving conception, but the exact mechanisms underlying such subfertility are still uncharacterized. Bongenaar et al. investigated the potential role in RA-associated female subfertility of interleukin (IL)-6 and tumour necrosis factor (TNF)-α, two pro-inflammatory mediators exerting a key pathogenic role. In a cohort of 61 RA women seeking a pregnancy, preconceptional IL-6 but not TNF-α levels predicted prolonged time to pregnancy, an association that held significance even after correction for confounders as disease activity.

The pivotal importance of optimal disease control reflects on the requirement of valid tools to evaluate disease activity even during pregnancy. Unfortunately, the reliability of conventional measures of disease activity in pregnant women is to be assessed: gestation may induce symptoms evaluated by these instruments and the physiological changes that occur in pregnancy may affect laboratory parameters used to assess disease activity, such as serum complement levels and C reactive protein (Andreoli et al., 2019). According to the data presented by Larosa et al., SLE disease activity score (SLE-DAS), a score composed by 17 items that has been recently proposed in SLE (Jesus et al., 2019), is a reliable tool to evaluate disease activity in pregnant lupus patients. SLE-DAS evaluated in 158 SLE women during the first trimester of gestation predicted maternal flares in the second and third trimesters (Larosa et al.).

Edited and reviewed by:
Catherine M. T. Sherwin, Wright State University, Dayton, United States

***Correspondence:**
Cecilia Beatrice Chighizola
cecilia.chighizola@unimi.it

Received: *10 September 2021*
Accepted: *03 November 2021*
Published: *26 November 2021*

Citation:
Chighizola CB, de Jesús GR, Gerosa M and Avčin T (2021) Editorial: Therapeutic Implications for Pregnant Women With Systemic Autoimmune Diseases and Their Children. Front. Pharmacol. 12:773970. doi: 10.3389/fphar.2021.773970

Similarly to SLE, autoimmune bullous diseases can manifest or exacerbate during pregnancy, as elegantly reviewed by the group of Marzano et al. The pharmacological approach to pregnant women with pemphigus and pemphigoid gestationis is challenging, and the therapeutic armamentarium includes systemic and topical corticosteroids, topical calcineurin inhibitors, dapsone, intravenous immunoglobulins, plasmapheresis/plasma exchange and biological agents.

The introduction of biologics has revolutionized the management of rheumatic diseases over the last decades; moreover, insights are being progressively gained on their use in pregnant women. Given their immunoglobulinic structure, biologics can cross the placenta from the 17th gestational week, when the Fc receptor becomes expressed. As outlined by Beltagy et al., inhibitors of TNF-α (in particular certolizumab and etanercept, as well as eculizumab, due to its engineered IgG2/4k molecular structure) are considered safe during gestational course. Carnovale et al. focused on agents targeting IL-1, together with colchicine, estimating maternal and fetal adverse events in a nested case-control study on data from the United States Food and Drug Administration Adverse Event Reporting System database. Reassuringly, the rates of pregnancy loss, fetal disorders, congenital defects, neonatal adverse events and delivery complications were not increased in women receiving inflammasome-targeted therapy (Carnovale et al.).

In women with rheumatic diseases, the above-cited Fc receptor mediates even the active transportation of maternal autoantibodies, some of which can induce a passively acquired autoimmune disease. This is the case of neonatal anti-phospholipid syndrome, an exceedingly rare condition in newborns. Paediatric rheumatologists describe four cases of stroke in neonates born to women with anti-phospholipid antibodies (Giani et al.). Three out of the four children had positive anti-ß2GPI and aCL IgG, which disappeared within 2 years of life and could be due to transplacental autoantibody transfer. One baby presented anti-ß2GPI IgM, while her mother tested negative for all aPL subtypes suggesting neonatal *de novo* production of aPL. The exact pathogenetic role of transmitted or *de novo* aPL in neonatal ischemic stroke is still unclear and may be linked with other genetic and acquired thrombophilic factors. Surely pharmacological treatment of rheumatic conditions in pregnant women allows a tighter disease control and, in turn, better obstetric and fetal outcomes. However, concerns have arisen about the potential long-term effects of *in utero* exposure to anti-rheumatic medications. A multi-disciplinary team of rheumatologists and child neuropsychiatrists investigated the impact of treatment during gestation in 18 school-age children born to 16 women with inflammatory arthritis. Neurodevelopmental issues were found to be more frequent in the offspring of patients with longer disease duration and those who were breastfed for less than 6 months (Nalli et al.). Lazzaroni et al. focused on the neuropsychiatric impact of exposure to azathioprine during fetal life in children born to women with SLE. In this prospective study, offspring of lupus patients had a similar neuropsychiatric outcome compared to the general pediatric population, and no difference emerged stratifying upon *in utero* exposure to azathioprine (Lazzaroni et al.).

These data are reassuring, further supporting the importance of appropriate prescription of available anti-rheumatic drugs to obtain disease control in pregnant patients. However, research efforts are still pursued to identify novel pharmacological targets. Yao et al. reviewed the relationship between maternal microbiome and obstetric complications such as preeclampsia. The microbiome in the mother's vagina and breast milk can also affect the development of neonatal nervous and immune systems (Yao et al.). Interestingly, not only gut microbiome undergoes several modifications during pregnancy and lactation, but also several pharmacological compounds commonly used in the treatment of inflammatory arthritis affect gut microbiome. Thus, as proposed by a Chinese group, the modulation of gut microbiome might affect disease activity in pregnant women with RA: prebiotics and probiotics, antibiotics, fecal microbiota transplantation and dietotherapy are among the potential strategies (Yao et al.).

As a whole, the manuscripts enclosed in the present research topic clearly highlight how rapidly the field is emerging: the times in which women with rheumatic diseases were discouraged from embarking in a pregnancy are luckily far away. Nevertheless, despite the much recent advancement, there are still many issues that should be unraveled to further improve the clinical management and the therapeutic approach to mothers-to-be as well as new mothers with rheumatologic conditions and their offspring.

AUTHOR CONTRIBUTIONS

All the authors contributed to writing the manuscript. All the authors approved the final draft of the manuscript.

REFERENCES

Andreoli, L., Gerardi, M. C., Fernandes, M., Bortoluzzi, A., Bellando-Randone, S., Brucato, A., et al. (2019). Disease Activity Assessment of Rheumatic Diseases during Pregnancy: a Comprehensive Review of Indices Used in Clinical Studies. *Autoimmun. Rev.* 18, 164–176. doi:10.1016/j.autrev.2018.08.008

Jesus, D., Matos, A., Henriques, C., Zen, M., Larosa, M., Iaccarino, L., et al. (2019). Derivation and Validation of the SLE Disease Activity Score (SLE-DAS): a New SLE Continuous Measure with High Sensitivity for Changes in Disease Activity. *Ann. Rheum. Dis.* 78, 365–371. doi:10.1136/annrheumdis-2018-214502

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

REVIEW
published: 08 May 2020
doi: 10.3389/fphar.2020.00643

The Role of Microbiomes in Pregnant Women and Offspring: Research Progress of Recent Years

Yao Yao[1†], Xiaoyu Cai[2†], Chunyan Chen[3], Hui Fang[4], Yunchun Zhao[1], Weidong Fei[1], Fengying Chen[1] and Caihong Zheng[1*]*

[1] Department of Pharmacy, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China, [2] Department of Pharmacy, Hangzhou First People's Hospital, Hangzhou, China, [3] Department of Pharmacy, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China, [4] Department of Pharmacy, The Affiliated Hospital of Hangzhou Normal University, Hangzhou, China

Pregnancy is a complicated and delicate process, the maternal body undergoes changes on hormones, immunity, and metabolism during pregnancy to support fetal development. Microbiomes in the human body mainly live in the intestine, and the human gut microbiomes are complex, which composed of more than 500 to 1500 different bacteria, archaea, fungi, and viruses. Studies have shown that these microbiomes are not only involved in the digestion and absorption of food but also indispensable in regulating host health. In recent years, there has been increasing evidence that microbiomes are important for pregnant women and fetuses. During pregnancy, there will be great changes in gut microbiomes. Regulating gut microbiomes is beneficial to the health of the mother and the fetus. In addition, many complications during pregnancy are related to gut microbiomes, such as gestational diabetes, obesity, preeclampsia, digestive disorders, and autoimmune diseases. Moreover, the microbiomes in mother's milk and vagina are closely related to the colonization of microbiomes in the early life of infants. In this review, we systematically review the role of maternal microbiomes in different gestational complications, and elucidate the function and mechanism of maternal microbiomes in the neural development and immune system of offspring. These will provide a clear knowledge framework or potential research direction for researchers in related fields.

Keywords: pregnancy, complication, microbiomes, offspring, mechanism

OPEN ACCESS

Edited by:
Tadej Avcin,
University Medical Centre Ljubljana, Slovenia

Reviewed by:
Jonathan Burton Wagner,
Children's Mercy Hospital, United States
Caren Lee Hughes,
Mayo Clinic, United States

***Correspondence:**
Yao Yao
yaoyaofb@zju.edu.cn
Caihong Zheng
chzheng@zju.edu.cn

†These authors share first authorship

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *21 February 2020*
Accepted: *22 April 2020*
Published: *08 May 2020*

Citation:
Yao Y, Cai X, Chen C, Fang H, Zhao Y, Fei W, Chen F and Zheng C (2020) The Role of Microbiomes in Pregnant Women and Offspring: Research Progress of Recent Years. Front. Pharmacol. 11:643. doi: 10.3389/fphar.2020.00643

INTRODUCTION

Pregnancy is a unique event with a lot of hormonal, immune, and metabolic changes in the body (Zhang et al., 2019). Some changes of the body during pregnancy may be closely related to the changes in the composition and diversity of gut microbiomes (GMs) (Barbour et al., 2007; Gohir et al., 2015; Khan et al., 2019). Changes in the composition and diversity of GMs may ultimately affect the host's immunity, metabolism, digestion, and neurodevelopment (Carding et al., 2015; Pedersen et al., 2016). Therefore, focusing on the GMs may yield a positive insight into pregnancy. The composition and diversity of the maternal GMs change progressively every 3 months of the

gestational period (Smid et al., 2018). However, GMs are basically unchanged during the first 3 months of pregnancy, such as Gram-positive and Gram-negative bacteria (de Brito Alves et al., 2019). The human gastrointestinal tract contains approximately 500~1,000 microbiomes and more than 3 million genotypes (Lozupone et al., 2012). The ratio of microbial cells to human cells is 10:1, and the genotype ratio is 100:1 (Vrieze et al., 2010). Researches showed that GMs play a vital role in human immunity and digestion, and are involved in the development of chronic diseases such as diabetes, hypertension, and inflammatory bowel disease (Hooper et al., 2012; Dolan and Chang, 2017; Lezutekong et al., 2018; Zhao et al., 2018). Increasing evidence indicated that the structure and composition of GMs are generally determined by the host's genetic factors, environmental factors, and dietary habits (David et al., 2014; Rothschild et al., 2018). During pregnancy, changes in the diversity and composition of GMs may occur naturally in multiple parts of the mother's body, including the oral cavity, vagina, intestine, and breast milk (Nuriel-Ohayon et al., 2016; Zhou and Xiao, 2018). However, the relationship between maternal GMs and the complex physiological conditions during pregnancy is still insufficiently discussed. Many scholars have begun to study the relationship between GMs imbalance and complications during pregnancy.

Gestational GMs are not only closely related to the health of pregnant women but also affect the health of offspring. The most important link between mother and fetus is the placenta, and placental microbiomes include *Tenericutes*, *Fusobacteria*, *Bacteroidetes*, and *Firmicutes*, all of which are nonpathogenic bacteria (Aagaard et al., 2014). However, factors such as maternal gestational diabetes, obesity, vaginal infections, and the use of antibiotics have led to changes in the composition of the placental microbiomes (Pelzer et al., 2017). For example, recent studies have reported that excessive weight gain during pregnancy is associated with risk factors such as disorders of placental microbiomes and preterm birth (Antony et al., 2015). In addition, in the postpartum environment, the relationship between the GMs of infant and breast milk microbiomes has also attracted increasing attention. A prospective study showed that the bacterial species in mother's breast milk are the most abundant in the GMs of offspring in the first month after the baby was born (Pannaraj et al., 2017), suggesting that breastfeeding is closely related to GMs of the infant in early life.

Therefore, it can be reasonably inferred that the strategy of regulating maternal GMs during the prenatal and early postnatal life of infants can be used as an innovative treatment method to prevent and/or control adverse maternal complications and offspring health. In this way, the use of probiotic interventions to regulate maternal microbiomes has become a safe strategy that can restore the community of symbiotic microbiomes and provide beneficial effects on maternal, fetal, and infant health (Sanz, 2011; Swartwout and Luo, 2018).

In this review, we introduce the role of GMs in different gestational complications and the function of maternal microbiomes in offspring. The factors that influence the microbiomes of pregnant women may provide a novel therapeutic target in the future. Understanding the adaptations of microbiomes and the mechanisms of how they can be modulated may be beneficial in gestational management.

THE ROLE OF GMs IN GESTATIONAL COMPLICATIONS

Gestational Diabetes Mellitus

There are two types of diabetes during pregnancy, however, only Gestational diabetes mellitus (GDM) is discussed within this section so we would simply omit the other type. GDM is diabetes with normal glucose metabolism or impaired glucose tolerance before pregnancy, which occurs or is diagnosed only during pregnancy and is associated with many adverse maternal and neonatal outcomes (Group et al., 2008; Schneider et al., 2011; American Diabetes, 2018). More than 80% of diabetic pregnant women have GDM, the incidence of GDM in countries around the world is reported as 1% to 14%, and the incidence rate in China is 1% to 5%, which has increased significantly in recent years (Sacks et al., 2012; Zhu and Zhang, 2016). GDM patients with glucose metabolism can return to normal after delivery, but they will have an increased chance of developing type 2 diabetes in the future (Lauenborg et al., 2004; Bellamy et al., 2009). The clinical course of diabetic pregnant woman is complex, both mother and child have risk, should be given attention (Vohr and Boney, 2008; Damm et al., 2016).

In recent years, the role of GMs in GDM has received increasing attention. Reports showed that, compared with pregnant women with normal blood sugar, the abundance of *Parabacteroides*, *Dialister*, *Akkermansia*, *Roseburia*, *Bacteroides*, *Methanobrevibacter smithii*, *Eubacterium species*, *Alistipes species*, *Bifidobacterium species* was reduced (Kuang et al., 2017; Cortez et al., 2019), and the abundance of *Firmicutes*, *Klebsiella variicola*, *Collinsella*, *Rothia*, *Ruminococcus*, *Actinobacteria*, *Parabacteroides distasonis*, *Desulfovibrio* was increased (Crusell et al., 2018; Ferrocino et al., 2018). Moreover, one study showed that placental microbiomes in patients with GDM changed significantly compared to those with normal blood sugar (Bassols et al., 2016). Compared with healthy pregnant women, the relative abundance of *Pseudomonadales order* and *Acinetobacter genus* in the intestinal flora of GDM patients is reduced. The GMs of patients diagnosed with GDM in the third trimester have previously exhibited a typical flora disorder, which persists even after about 8 months postpartum (Crusell et al., 2018). These data suggest that GMs may play an important role in GDM. Adverse pregnancy complications in pregnant women are closely related to intestinal permeability, such as GDM, insulin resistance, inflammatory response and hyperglycemia (Flint et al., 2012; Navab-Moghadam et al., 2017). In general, the imbalance of GMs is the main cause of impaired intestinal permeability (Navab-Moghadam et al., 2017). In addition, the study by Bassols et al. showed that the reduced relative abundance of *Acinetobacter genus* is related to a decrease in

the blood eosinophil count and a decrease in the expression of several antiinflammatory cytokines in the placenta, such as metallopeptidase inhibitor 3 and IL-10 (Bassols et al., 2016). Therefore, GMs may predict the development and prognosis of GDM. Properly regulating the GMs of pregnant women may be an effective method for the treatment of GDM. However, relevant mechanistic or interventional trials are still lacking and further prospective trials are needed.

Gestational Obesity

Gestational obesity generally refers to obesity caused by a woman's weight gain exceeding the normal weight gain range during pregnancy. Gestational obesity can be divided into two phases: obesity during pregnancy and postpartum obesity (postpartum weight retention). The standards adopted by the American Institute of Medical Research (IOM) in 2009 are used in China to determine whether the degree of weight gain during pregnancy is abnormal (**Table 1**). Gestational obesity not only adversely affects pregnant women, but also the fetus, including GDM, hypertension during pregnancy, subinvolution of uterus, giant baby, and neonatal congenital defects (Poston et al., 2016; Zambrano et al., 2016).

Over the past few decades, it has been generally agreed that the main factor associated with gestational obesity is hormones. However, in recent years, the relationship between GMs and gestational obesity has received widespread attention. GMs during pregnancy can be regarded as a metabolic organ of the human body, and its imbalance may cause obesity and related metabolic disorders (Kalliomaki et al., 2008). A prospective follow-up study showed that excessive weight gain during pregnancy was associated with a high concentration of *Bacteroides* spp. in the intestine (Collado et al., 2008). Santacruz et al. found that in the gut of overweight pregnant women, the abundance of *Enterobacteriaceae* and *Escherichia coli* decreased significantly, while the abundance of *Bacteroides* and *Bifidobacterium* increased (Santacruz et al., 2010). The study further showed that the abundance of these microbiomes is related to weight gain and biochemical parameters such as transferrin, high-density lipoprotein cholesterol, triglycerides, plasma cholesterol, and folic acid. These studies indicate that GMs are closely related to gestational obesity, and the intestine may be an important organ for regulating maternal lipid metabolism. Therefore, regulating GMs to improve maternal obesity may be a promising and novel strategy, and further prospective trials are needed.

TABLE 1 | Criteria for obesity during pregnancy in China.

Weight status before pregnancy	Weight gain during pregnancy		
	Insufficient weight gain during pregnancy (kg)	Normal gain during pregnancy (kg)	Overweight gain during pregnancy (Gestational obesity) (kg)
Thin	<12.5	12.5~18.0	>18.0
Normal	<11.5	11.5~16.0	>16.0
Overweight	<7.0	7.0~11.5	>11.5
Fat	<5.0	5.0~9.0	>9.0

However, the mechanism by which GMs improve gestational obesity is not clear. By consulting the literature, we have compiled the possible mechanisms that currently exist as follows (Collado et al., 2008; Kumar et al., 2014; Barlow et al., 2015; Khan et al., 2016; Soderborg et al., 2016; Gu et al., 2017): (1) Chronic inflammation results in endotoxin released into the blood after bacterial death leading to endotoxemia. For example, lipopolysaccharides (cell wall components of Gram-negative bacteria) are closely related to insulin resistance and inflammatory responses. (2) Disorder of GMs alters epigenetic modifications. (3) Decreased probiotics and increased harmful bacteria may increase the intestinal capacity for absorption and monosaccharide uptake. (4) Changes in gut microbial metabolites. For example, bacterial metabolites SCFAs can regulate hormone metabolism, inhibit the body's inflammatory response, and change the composition of intestinal immune cells. (5) Certain GMs can inhibit the production of adipose cytokines induced by fasting, which can inhibit protein lipase, leading to the accumulation of fat in peripheral tissues to form obesity. (6) Activation of liver endocannabinoid (eCB) and ChREBP/SREBP-1system. (7) Metabolism of primary bile acids in the small intestine to secondary bile acids.

In summary, GMs play a crucial role in gestational obesity, but its mechanism remains to be further explored. Taking advantage of the double-edged sword of GMs may yield unexpected results in managing gestational obesity.

Preeclampsia

Preeclampsia refers to increased blood pressure and proteinuria after 20 weeks of pregnancy, and symptoms such as headache, dizziness, nausea, vomiting, and epigastric discomfort may also occur (Brown et al., 2018). It is the second leading cause of maternal death in the world currently (Huppertz, 2008; Ghulmiyyah and Sibai, 2012; Mol et al., 2016). The incidence of preeclampsia is about 5% of pregnant women, and it is more common in primiparas and pregnant women with hypertension and vascular disease (Hutcheon et al., 2011; Ananth et al., 2013). The cause of preeclampsia is not yet clear. At present, the related risk factors are weight, pregnancy hypertension, first pregnancy, age, and history of preeclampsia. However, the combination of these risk factors can only predict the occurrence of preeclampsia in clinical practice in 30% of pregnant women (Odibo et al., 2015; Mol et al., 2016).

In recent years, great breakthroughs have been made in the etiology of preeclampsia with the efforts of researchers. The study by Kell et al. has shown that the mechanisms leading to the development of preeclampsia include abnormal trophoblast invasion into the placenta, oxidative stress, antiangiogenic response, and increased proinflammatory cytokines (Kell and Kenny, 2016). In addition, researchers have found that the placenta plays a key role in the pathogenesis of preeclampsia and adversely affects the fetus. This may be due to obstructed utero-placental blood flow, which increases the risk of preterm and low birth weight fetuses (Salmani et al., 2014; Ilekis et al., 2016; Carter et al., 2017).

In addition to the above, GMs have recently been linked to the etiology of preeclampsia. The identification of placental

microbiomes in pregnant women with preeclampsia indicates the abundance of several types of bacteria in the placenta is related to gastrointestinal infection, respiratory infection or periodontitis, respectively. For example, *Escherichia*, *Bacillus*, *Salmonella*, and *Listeria* are associated with gastrointestinal infections, *Anoxybacillus*, and *Klebsiella* are associated with respiratory infections, *Dialiste*, *Variovorax*, *Porphyromonas*, and *Prevotella shahii* are associated with periodontitis (Amarasekara et al., 2015). In addition, studies have shown that the abundance of pathogenic bacteria (*Bulleidia moorei* and *Clostridium perfringens*) in the intestine of preeclampsia women is increased, while the abundance of probiotics (*Coprococcus catus*) is decreased compared with healthy pregnant women (Lv et al., 2019). The above evidences suggest that: (1) The imbalance of placental microbiomes may be closely related to the occurrence and development of preeclampsia. (2) GMs play a vital role in the preeclampsia of pregnant women. Therefore, detecting intestinal and placental microbiomes in pregnant women with preeclampsia may provide a new idea for improving clinical symptoms. In addition, probiotic interventions may be an effective way to protect pregnant women from suffering headaches, dizziness, nausea, or vomiting. However, the above data only show that GMs is related to preeclampsia, and the specific mechanism remains to be further explored.

Disease of Digestive Tract

The most common digestive tract diseases are tumors, as well as enteritis and gastritis. But the scope of our discussion here does not include tumors. Studies have reported that digestive tract management during pregnancy is the most challenging for gastroenterologists, at which time multiple reactions occur in the gastrointestinal tract, such as esophageal reflux, constipation, nausea, and vomiting (McCarthy et al., 2014). The incidence of vomiting during pregnancy is about 50%, and the incidence of nausea is about 50% to 80% (Matthews et al., 2015). A few pregnant women have severe early pregnancy reactions, frequent nausea, and vomiting, resulting in fluid imbalance and metabolic disorders, and even endanger the life of pregnant women, which is called hyperemesis gravidarum and the incidence is about 1.2% (Einarson et al., 2013). At present, the treatment of digestive tract diseases during pregnancy is mostly symptomatic, and the mechanism of their occurrence is unclear.

Studies on the relationship between digestive tract diseases and GMs have been available in the past, but few have studied the relationship between digestive tract diseases during pregnancy and GMs. Recent studies have shown that the relative abundance of *Blautia* and *Collinsella* in the intestine of pregnant women with gastrointestinal disorders is significantly reduced, and the abundance of *Acinetobacter*, *Enterococci*, and *Paenibacillus* is increased. The author further revealed that *Blautia* and *Collinsella* may be served as a new biomarker for digestive disorders in pregnancy (Jin et al., 2019). In addition, increasing evidences indicate that disorders of the maternal GMs increase the prevalence of colitis in the offspring in adulthood. Xie et al. found that high-fat diets in mice during pregnancy altered the intestinal flora of offspring and exacerbated dextran sodium sulfate (DSS)–induced colitis in offspring (Xie et al., 2018). Adult mice colonized with *Lactobacillus rhamnosus* (LGG) showed increased IgA production and decreased susceptibility to intestinal injury and inflammation induced in the dextran sodium sulphate model of colitis. Thus, neonatal colonization of mice with LGG enhances intestinal functional maturation and IgA production, and confers lifelong health consequences on protection from intestinal injury and inflammation (Yan et al., 2017). Not only that, a population-based cohort study suggested that exposure to antibiotics during pregnancy increases the risk of offspring from inflammatory bowel disease (Ortqvist et al., 2019).

To sum up, the GMs are closely related to maternal and offspring digestive tract diseases. However, the role of GMs in maternal digestive tract diseases has not yet been clearly elucidated. The effect of maternal GMs on offspring's digestive tract disease is well established. Improving the GMs imbalance during pregnancy and strengthening the management and monitoring of GMs may be a potential method for treating digestive diseases in pregnancy, which will reduce the probability of offspring suffering from digestive diseases.

Autoimmune Diseases

Autoimmune diseases refer to the disease caused by the body's immune response to autoantigen, which leads to auto tissue damage such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (Davidson and Diamond, 2001; Yao et al., 2018; Yao et al., 2019). There are more than 70 diseases classified as autoimmune diseases at present, and their prevalence in the general population is about 7% (Cooper et al., 2009). Many autoimmune diseases have a significantly higher incidence in women than men, including SLE and RA, which may be caused by female sex hormones regulating the immune system through sex hormone receptors (Adams Waldorf and Nelson, 2008; Cai et al., 2019; Tsao et al., 2019). During pregnancy, the mother undergoes a series of physiological changes to ensure the healthy growth of the fetus, including immune, hormonal, and metabolic changes (Kumar and Magon, 2012). In recent years, more and more evidences showed that there is a correlation between pregnancy and autoimmune diseases (Tincani et al., 2016).

Among the many factors related to pregnancy affecting autoimmune diseases, GMs have attracted widespread attention. It has been reported that the imbalance of GMs is associated with a variety of autoimmune diseases, such as SLE and RA (Mu et al., 2015). On the one hand, GMs disorder does exist in animal models (adjuvant arthritis model, collagen-induced arthritis model, lupus-prone mouse model) and human patients (Hevia et al., 2014; Zhang et al., 2014; Luo et al., 2018). On the other hand, the use of probiotics and antibiotics has been shown to regulate GMs (Mu et al., 2017a; Mu et al., 2017b; Manfredo Vieira et al., 2018). In a study of SLE, the authors found that changes in the GMs during pregnancy and lactation interfered with the autoimmune response (Mu et al., 2019). However, the study did not explore the mechanism of changes in GMs during pregnancy in SLE. Therefore, further prospective or interventional studies are needed to better understand the complex relationship between pregnancy and

lupus. According to these reports, we speculate that intestinal microbiomes are closely related to RA in pregnancy, even though there are no published reports. A study on RA revealed that a single bacterium restores microbiomes imbalances to protect the bones of RA rats from damage (Pan et al., 2019). In addition, changes in the composition and structure of the GMs during pregnancy have been well recognized. Therefore, it is of far-reaching clinical significance to explore the role and mechanism of GMs in pregnancy with autoimmune diseases. GMs intervention for pregnant women with autoimmune disease may be a new clinical treatment, and further prospective trials are needed.

THE ROLE OF MATERNAL MICROBIOMES IN OFFSPRING

Effects of Maternal Microbiomes on the Offspring's Immune System

Maternal microbiomes are not only closely related to gestational complications, they are also vital to the health of the fetus. The development of babies' GMs is related to the existing microbiomes in many parts of mother's body. The microbiomes in these parts of the mother's body can be transmitted vertically to offspring, including the intestine, skin, breast milk, and vagina (Nyangahu et al., 2018). Studies have shown that the most significant periods are childbirth and postpartum, especially when infants are exposed to maternal skin, vagina, and feces (Mackie et al., 1999). In previous research, the idea that the uterine environment was sterile (Funkhouser and Bordenstein, 2013) has been questioned in recent years (Jimenez et al., 2008). Theis et al. found there are unique microbiomes in the placenta, which have not been reported before (Theis et al., 2019). However, recent evidence suggests that the microbiomes of pregnant women have a strong effect on the progeny microbiomes, whether or not placental microbiomes are actually present. Studies have expounded that the mother's GMs can better adapt to the baby's gut environment and live longer compared to nonmaternally derived flora (Ferretti et al., 2018). A mouse experiment also showed most of the bacteria in the meconium sample matched the mother's oral bacterial sample (genetically labeled) (Jimenez et al., 2008). These data reveal the importance of maternal microbiomes (not just GMs) to the fetus.

Furthermore, studies have shown that transient changes in maternal microbiomes during pregnancy drive the fetus's immune planning (Gomez de Aguero et al., 2016). A perinatal study showed that after treating pregnant mice with a large number of antibiotics, their offspring lacked IL-17–producing cells and IL-17 transcripts in the small intestine (Deshmukh et al., 2014). Similarly, in another study, after treating pregnant mice with three antibiotics, the offspring's GMs diversity reduced, and IL-17-IFN-γ–producing $CD4^+$ and $CD8^+$ cells in mesenteric lymph nodes decreased (Hu et al., 2015). These indicate that maternal microbiomes play an important role in enteric immune system of offspring.

In addition to the effects on the baby's enteric immune system, maternal microbiomes also affect the offspring's peripheral immune system. Gonzalez-Perez et al. observed that after treatment of dams with antibiotics during pregnancy and lactation, their pups lacked production of IFN-γ by $CD8^+$ T cells, and the distribution of dendritic cells and NK cell subsets changed (Gonzalez-Perez et al., 2016). In a mouse model of autoimmunity based on the NLRP3 inflammasome mutation R258W, the maternal microbiomes were required for neonatal IL-1β and tumor necrosis factor-a (TNF-α) responses in the skin (Nakamura et al., 2012). The effect of perinatal maternal microbiomes on the immune system of offspring may be due to the effect of microbiomes on the development of immune cells (Josefsdottir et al., 2017). Joana Torres et al. found that aberrant microbiomes composition persists during pregnancy with IBD and alters the bacterial diversity and abundance in the infant stool (Torres et al., 2020). The research of Nyangahu et al. indicates that perturbations to maternal microbiomes dictate neonatal adaptive immunity (Nyangahu et al., 2018).

Therefore, from the data above, it can be seen that maternal microbiomes play a vital role in the offspring's immune system. Regulating the microbiomes of pregnant women is of great significance to the offspring's health, which may provide a novel insight into the management of pregnant women in clinical practice.

Effects of Maternal Microbiomes on the Offspring's Neurodevelopment

The relationship between the gastrointestinal environment and the state of brain has been proven in the past, but the existence of the microbial-gut-brain axis has only received attention in the last decade (Bienenstock et al., 2015). There are many microbiomes are symbiotic with humans, these symbiotic microbiomes and their microbial groups are closely related to the host's brain and nerve development (Dinan and Cryan, 2017). In recent years, scholars found that the structural changes of microbiomes in the host are related to their neurological disorders, such as anxiety, autism, depression, and stress (Vuong and Hsiao, 2017). As early as 30 years ago, the role of the perinatal environment in heredity attracted attention, which could affect the offspring's health in adulthood (Barker, 2004). By understanding the Barker hypothesis, it has recently been further suggested that perinatal microbiomes play an important role in planning adult brain health (Codagnone et al., 2019).

Not only that, increasing evidence reveals microbiomes are critical in host neurodevelopment. A study of germ-free mice showed that the lack of regulatory effects of microbiomes leads to abnormal brain development in mice, such as abnormal growth of microglia, high myelinization of the prefrontal cortex, and increased permeability of the blood-brain barrier (Clarke et al., 2013; Braniste et al., 2014; Thion et al., 2018). In microbial deficiency mice, the expression of genes related to neural development is affected, including neuronal plasticity and neurotransmission in the hippocampus (Stilling et al., 2015; Chen et al., 2017). These changes in neurophysiology will

eventually translate into anxiety, increased stress response, cognitive deficits, visceral pain response, and changes in fear (Gareau et al., 2011; Luczynski et al., 2017; Hoban et al., 2018). In addition, studies showed that changes in the structure of perinatal microbiomes regulate gene expression, function, and morphology of progeny microglia, these effects will appear in the early stages of embryo development. These data reveal that the colonization of microbiomes in early life has a huge impact on the neural development and function of offspring.

In terms of genetic research about maternal microbiomes, experiments indicated that microglial status can be regulated in microbially depleted mice during adulthood, and three independent studies emphasized the role of maternal microbiomes in guiding embryonic microglial development. What's more, the gene expression changes of germ-free mouse microglia were more obvious in adult microglia than in neonatal microglia compared with the conventional control group (Matcovitch-Natan et al., 2016). These findings suggest that microbiomes are important for microglia development from adulthood to adult phenotype. Nonetheless, 240 genes are expressed differently even in newborn microglia, suggesting that the maternal microbiomes may direct microglia maturation during prenatal development. Consistent with this, 19 differentially expressed genes were detected in microglial cells harvested from germ-free embryo (14.5-day-old), indicating that the maternal microbiomes have little effect on microglial progenitor cells (Thion et al., 2018). So, why are there differences of opinion on the effects of maternal microbiomes on offspring? The main reason is that the research phase of pregnancy is different. It is now widely believed that the moment of birth is the first opportunity for large-scale colonization of neonatal bacteria (Biasucci et al., 2008; Backhed et al., 2015). Therefore, the mode of delivery has a huge impact on the establishment of infant microflora. Numerous studies have begun to link childbirth patterns to the unique trajectories of neonatal microbial development (Biasucci et al., 2008; Backhed et al., 2015). Studies revealed that newborns born by cesarean section (without exposure to the birth canal) at birth are unable to obtain vertical transmission of bacteria and viruses from the mother's vagina (Backhed et al., 2015; McCann et al., 2018). In addition, it should be emphasized that the changes in the progeny microbial structure due to different delivery methods are temporary. However, the composition and abundance of intestinal micro-organisms in infants born by vaginal delivery are significantly higher than those in newborns born by cesarean section (Biasucci et al., 2008; Azad et al., 2013; Jakobsson et al., 2014; McCann et al., 2018).

So, how do microbiomes affect the neurodevelopment of offspring? The possible mechanisms are as follows: (1) Toll-like Receptors (TLRs) signaling on neuronal proliferation: TLRs can perform innate immune recognition on the components of microbiomes; TLRs are expressed in all subtypes of brain resident cells, including intact expression in astrocytes, neurons, and oligodendrocytes (Hanke and Kielian, 2011; Kawai and Akira, 2011). (2) Cytokine signaling on neurogenesis: In the brain, cytokines have different effects on neurodevelopment. For example, IL-4 inhibits the proliferation of mouse embryonic neural precursor cells (NPCs), IL-34 and CSF-1 promote neuronal proliferation, and IL-6 promotes the occurrence of fetal striatum cells; maternal intestinal microbiomes can fully change germ-free mouse intestinal cytokines distributed (Pronovost and Hsiao, 2019). (3) Complement proteins in synaptic refinement: The complement system contributes to the clarity of cells and humoral-mediated pathogenic microbiomes (Ricklin et al., 2016). Synaptic complement proteins play an important role in the early development of neurons. For example, complement protein C3 is localized to the axons of retinal geniculate cells and depends on upstream complement proteins C1 and C4 (Sekar et al., 2016).

CONCLUSION

In summary, GMs play a vital role in a variety of complications in pregnant women. Current researches reveal that the abundance and composition of some GMs are altered during pregnancy complications. Maternal GMs could affect pregnant women's physiological metabolism, immune system or inflammatory response (**Table 2**). However, in terms of impact on offspring, it is thought that the effect of maternal GMs on the fetus is not

TABLE 2 | Changes of gut microbiomes in pregnancy complications and its mechanisms.

Complications of pregnancy	Increased abundance of microorganisms	Decreased abundance of microorganisms	Mechanisms	References
Gestational diabetes	*Firmicutes, Klebsiella variicola, Collinsella, Rothia, Ruminococcus, Actinobacteria, Parabacteroides distasonis, Desulfovibrio*	*Parabacteroides, Dialister, Akkermansia, Roseburia, Methanobrevibacter smithii, Eubacterium species, Alistipes species, Bacteroides Bifidobacterium species*	Intestinal permeability, anti-inflammatory cytokine levels, etc.	Bassols et al., 2016; Navab-Moghadam et al., 2017; Crusell et al., 2018; Ferrocino et al., 2018
Gestational obesity	*Bacteroides, Bifidobacterium*	*Enterobacteriaceae, Escherichia coli*	Microbial metabolites, inflammatory responses, epigenetic modifications, etc.	Santacruz et al., 2010; Barlow et al., 2015; Khan et al., 2016; Soderborg et al., 2016; Gu et al., 2017; Collado et al., 2008
Preeclampsia	*Bulleidia moorei, Clostridium perfringens*	*Coprococcus catus*	Future research is needed	Lv et al., 2019
Disease of digestive tract	*Acinetobacter*, *Enterococci*, *Paenibacillus*	*Blautia, Collinsella*	Future research is needed	Jin et al., 2019
Autoimmune disease	*Firmicutes, Acholeplasmatales, Desulfovibrionales*	*Verrucomicrobia, Bacteroidales,*	Autoimmune response	Pan et al., 2019

significant. Maternal microbiomes that affect offspring are mainly those in the vagina or milk. In addition, the mode of childbirth is also important for the colonization of microbiomes in the baby, because the moment of birth is the first opportunity for large-scale colonization of neonatal bacteria. Nevertheless, the transmission of maternal microbiomes is closely related to the offspring's immune system and neurodevelopment. Therefore, exploring the role and mechanism of GMs in pregnancy complications and offspring is very meaningful for managing their health. The limitation here is that most of the current studies on the role of maternal microbiomes in pregnancy complications or offspring are only relevance studies, and still in infancy, further mechanistic and interventional trials or prospective studies are needed.

AUTHOR CONTRIBUTIONS

YY and XC drafted the manuscript. CC, YZ, HF, and FC modified the manuscript. WF and CZ edited and added valuable insights into the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

FUNDING

This study was supported by the National Natural Science Foundation of China (Grant Nos. 81873838, 81802630).

REFERENCES

Aagaard, K., Ma, J., Antony, K. M., Ganu, R., Petrosino, J., and Versalovic, J. (2014). The placenta harbors a unique microbiome. *Sci. Transl. Med.* 6, 237ra265. doi: 10.1126/scitranslmed.3008599

Adams Waldorf, K. M., and Nelson, J. L. (2008). Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol. Invest.* 37, 631–644. doi: 10.1080/08820130802205886

Amarasekara, R., Jayasekara, R. W., Senanayake, H., and Dissanayake, V. H. (2015). Microbiome of the placenta in pre-eclampsia supports the role of bacteria in the multifactorial cause of pre-eclampsia. *J. Obstet. Gynaecol. Res.* 41, 662–669. doi: 10.1111/jog.12619

American Diabetes, A. (2018). Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 41, S13–S27. doi: 10.2337/dc18-S002

Ananth, C. V., Keyes, K. M., and Wapner, R. J. (2013). Pre-eclampsia rates in the United States 1980-2010: age-period-cohort analysis. *BMJ* 347, f6564. doi: 10.1136/bmj.f6564

Antony, K. M., Ma, J., Mitchell, K. B., Racusin, D. A., Versalovic, J., and Aagaard, K. (2015). The preterm placental microbiome varies in association with excess maternal gestational weight gain. *Am. J. Obstet. Gynecol.* 212, 653, e651–e616. doi: 10.1016/j.ajog.2014.12.041

Azad, M. B., Konya, T., Maughan, H., Guttman, D. S., Field, C. J., Chari, R. S., et al. (2013). Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *CMAJ* 185, 385–394. doi: 10.1503/cmaj.121189

Backhed, F., Roswall, J., Peng, Y., Feng, Q., Jia, H., Kovatcheva-Datchary, P., et al. (2015). Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. *Cell Host. Microbe* 17, 852. doi: 10.1016/j.chom.2015.04.004

Barbour, L. A., McCurdy, C. E., Hernandez, T. L., Kirwan, J. P., Catalano, P. M., and Friedman, J. E. (2007). Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care* 30 Suppl 2, S112–S119. doi: 10.2337/dc07-s202

Barker, D. J. (2004). The developmental origins of adult disease. *J. Am. Coll. Nutr.* 23, 588S–595S. doi: 10.1080/07315724.2004.10719428

Barlow, G. M., Yu, A., and Mathur, R. (2015). Role of the Gut Microbiome in Obesity and Diabetes Mellitus. *Nutr. Clin. Pract.* 30, 787–797. doi: 10.1177/0884533615609896

Bassols, J., Serino, M., Carreras-Badosa, G., Burcelin, R., Blasco-Baque, V., Lopez-Bermejo, A., et al. (2016). Gestational diabetes is associated with changes in placental microbiota and microbiome. *Pediatr. Res.* 80, 777–784. doi: 10.1038/pr.2016.155

Bellamy, L., Casas, J. P., Hingorani, A. D., and Williams, D. (2009). Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 373, 1773–1779. doi: 10.1016/S0140-6736(09)60731-5

Biasucci, G., Benenati, B., Morelli, L., Bessi, E., and Boehm, G. (2008). Cesarean delivery may affect the early biodiversity of intestinal bacteria. *J. Nutr.* 138, 1796S–1800S. doi: 10.1093/jn/138.9.1796S

Bienenstock, J., Kunze, W., and Forsythe, P. (2015). Microbiota and the gut-brain axis. *Nutr. Rev.* 73 Suppl 1, 28–31. doi: 10.1093/nutrit/nuv019

Braniste, V., Al-Asmakh, M., Kowal, C., Anuar, F., Abbaspour, A., Toth, M., et al. (2014). The gut microbiota influences blood-brain barrier permeability in mice. *Sci. Transl. Med.* 6, 263ra158. doi: 10.1126/scitranslmed.3009759

Brown, M. A., Magee, L. A., Kenny, L. C., Karumanchi, S. A., McCarthy, F. P., Saito, S., et al. (2018). Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management Recommendations for International Practice. *Hypertension* 72, 24–43. doi: 10.1161/HYPERTENSIONAHA.117.10803

Cai, X., Zhang, L., and Wei, W. (2019). Regulatory B cells in inflammatory diseases and tumor. *Int. Immunopharmacol.* 67, 281–286. doi: 10.1016/j.intimp.2018.12.007

Carding, S., Verbeke, K., Vipond, D. T., Corfe, B. M., and Owen, L. J. (2015). Dysbiosis of the gut microbiota in disease. *Microb. Ecol. Health Dis.* 26, 26191. doi: 10.3402/mehd.v26.26191

Carter, E. B., Conner, S. N., Cahill, A. G., Rampersad, R., Macones, G. A., and Tuuli, M. G. (2017). Impact of fetal growth on pregnancy outcomes in women with severe preeclampsia. *Pregnancy Hypertens.* 8, 21–25. doi: 10.1016/j.preghy.2017.02.002

Chen, J. J., Zeng, B. H., Li, W. W., Zhou, C. J., Fan, S. H., Cheng, K., et al. (2017). Effects of gut microbiota on the microRNA and mRNA expression in the hippocampus of mice. *Behav. Brain Res.* 322, 34–41. doi: 10.1016/j.bbr.2017.01.021

Clarke, G., Grenham, S., Scully, P., Fitzgerald, P., Moloney, R. D., Shanahan, F., et al. (2013). The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol. Psychiatry* 18, 666–673. doi: 10.1038/mp.2012.77

Codagnone, M. G., Spichak, S., O'Mahony, S. M., O'Leary, O. F., Clarke, G., Stanton, C., et al. (2019). Programming Bugs: Microbiota and the Developmental Origins of Brain Health and Disease. *Biol. Psychiatry* 85, 150–163. doi: 10.1016/j.biopsych.2018.06.014

Collado, M. C., Isolauri, E., Laitinen, K., and Salminen, S. (2008). Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *Am. J. Clin. Nutr.* 88, 894–899. doi: 10.1093/ajcn/88.4.894

Cooper, G. S., Bynum, M. L., and Somers, E. C. (2009). Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. *J. Autoimmun.* 33, 197–207. doi: 10.1016/j.jaut.2009.09.008

Cortez, R. V., Taddei, C. R., Sparvoli, L. G., Angelo, A. G. S., Padilha, M., Mattar, R., et al. (2019). Microbiome and its relation to gestational diabetes. *Endocrine* 64, 254–264. doi: 10.1007/s12020-018-1813-z

Crusell, M. K. W., Hansen, T. H., Nielsen, T., Allin, K. H., Ruhlemann, M. C., Damm, P., et al. (2018). Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. *Microbiome* 6, 89. doi: 10.1186/s40168-018-0472-x

Damm, P., Houshmand-Oeregaard, A., Kelstrup, L., Lauenborg, J., Mathiesen, E. R., and Clausen, T. D. (2016). Gestational diabetes mellitus and long-term consequences for mother and offspring: a view from Denmark. *Diabetologia* 59, 1396–1399. doi: 10.1007/s00125-016-3985-5

David, L. A., Maurice, C. F., Carmody, R. N., Gootenberg, D. B., Button, J. E., Wolfe, B. E., et al. (2014). Diet rapidly and reproducibly alters the human gut microbiome. *Nature* 505, 559–563. doi: 10.1038/nature12820

Davidson, A., and Diamond, B. (2001). Autoimmune diseases. *N. Engl. J. Med.* 345, 340–350. doi: 10.1056/NEJM200108023450506

de Brito Alves, J. L., de Oliveira, Y., Carvalho, N. N. C., Cavalcante, R. G. S., Pereira Lira, M. M., Nascimento, L., et al. (2019). Gut microbiota and probiotic intervention as a promising therapeutic for pregnant women with cardiometabolic disorders: Present and future directions. *Pharmacol. Res.* 145, 104252. doi: 10.1016/j.phrs.2019.104252

Deshmukh, H. S., Liu, Y., Menkiti, O. R., Mei, J., Dai, N., O'Leary, C. E., et al. (2014). The microbiota regulates neutrophil homeostasis and host resistance to Escherichia coli K1 sepsis in neonatal mice. *Nat. Med.* 20, 524–530. doi: 10.1038/nm.3542

Dinan, T. G., and Cryan, J. F. (2017). Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. *J. Physiol.* 595, 489–503. doi: 10.1113/JP273106

Dolan, K. T., and Chang, E. B. (2017). Diet, gut microbes, and the pathogenesis of inflammatory bowel diseases. *Mol. Nutr. Food Res.* 61. doi: 10.1002/mnfr.201600129

Einarson, T. R., Piwko, C., and Koren, G. (2013). Prevalence of nausea and vomiting of pregnancy in the USA: a meta analysis. *J. Popul. Ther. Clin. Pharmacol.* 20, e163–e170.

Ferretti, P., Pasolli, E., Tett, A., Asnicar, F., Gorfer, V., Fedi, S., et al. (2018). Mother-to-Infant Microbial Transmission from Different Body Sites Shapes the Developing Infant Gut Microbiome. *Cell Host. Microbe* 24, 133–145 e135. doi: 10.1016/j.chom.2018.06.005

Ferrocino, I., Ponzo, V., Gambino, R., Zarovska, A., Leone, F., Monzeglio, C., et al. (2018). Changes in the gut microbiota composition during pregnancy in patients with gestational diabetes mellitus (GDM). *Sci. Rep.* 8, 12216. doi: 10.1038/s41598-018-30735-9

Flint, H. J., Scott, K. P., Louis, P., and Duncan, S. H. (2012). The role of the gut microbiota in nutrition and health. *Nat. Rev. Gastroenterol. Hepatol.* 9, 577–589. doi: 10.1038/nrgastro.2012.156

Funkhouser, L. J., and Bordenstein, S. R. (2013). Mom knows best: the universality of maternal microbial transmission. *PloS Biol.* 11, e1001631. doi: 10.1371/journal.pbio.1001631

Gareau, M. G., Wine, E., Rodrigues, D. M., Cho, J. H., Whary, M. T., Philpott, D. J., et al. (2011). Bacterial infection causes stress-induced memory dysfunction in mice. *Gut* 60, 307–317. doi: 10.1136/gut.2009.202515

Ghulmiyyah, L., and Sibai, B. (2012). Maternal mortality from preeclampsia/eclampsia. *Semin. Perinatol.* 36, 56–59. doi: 10.1053/j.semperi.2011.09.011

Gohir, W., Whelan, F. J., Surette, M. G., Moore, C., Schertzer, J. D., and Sloboda, D. M. (2015). Pregnancy-related changes in the maternal gut microbiota are dependent upon the mother's periconceptional diet. *Gut. Microbes* 6, 310–320. doi: 10.1080/19490976.2015.1086056

Gomez de Aguero, M., Ganal-Vonarburg, S. C., Fuhrer, T., Rupp, S., Uchimura, Y., Li, H., et al. (2016). The maternal microbiota drives early postnatal innate immune development. *Science* 351, 1296–1302. doi: 10.1126/science.aad2571

Gonzalez-Perez, G., Hicks, A. L., Tekieli, T. M., Radens, C. M., Williams, B. L., and Lamouse-Smith, E. S. (2016). Maternal Antibiotic Treatment Impacts Development of the Neonatal Intestinal Microbiome and Antiviral Immunity. *J. Immunol.* 196, 3768–3779. doi: 10.4049/jimmunol.1502322

Group, H. S. C. R., Metzger, B. E., Lowe, L. P., Dyer, A. R., Trimble, E. R., Chaovarindr, U., et al. (2008). Hyperglycemia and adverse pregnancy outcomes. *N. Engl. J. Med.* 358, 1991–2002. doi: 10.1056/NEJMoa0707943

Gu, Y., Wang, X., Li, J., Zhang, Y., Zhong, H., Liu, R., et al. (2017). Analyses of gut microbiota and plasma bile acids enable stratification of patients for antidiabetic treatment. *Nat. Commun.* 8, 1785. doi: 10.1038/s41467-017-01682-2

Hanke, M. L., and Kielian, T. (2011). Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. *Clin. Sci. (Lond)* 121, 367–387. doi: 10.1042/CS20110164

Hevia, A., Milani, C., Lopez, P., Cuervo, A., Arboleya, S., Duranti, S., et al. (2014). Intestinal dysbiosis associated with systemic lupus erythematosus. *mBio* 5, e01548–e01514. doi: 10.1128/mBio.01548-14

Hoban, A. E., Stilling, R. M., Moloney, G., Shanahan, F., Dinan, T. G., Clarke, G., et al. (2018). The microbiome regulates amygdala-dependent fear recall. *Mol. Psychiatry* 23, 1134–1144. doi: 10.1038/mp.2017.100

Hooper, L. V., Littman, D. R., and Macpherson, A. J. (2012). Interactions between the microbiota and the immune system. *Science* 336, 1268–1273. doi: 10.1126/science.1223490

Hu, Y., Peng, J., Tai, N., Hu, C., Zhang, X., Wong, F. S., et al. (2015). Maternal Antibiotic Treatment Protects Offspring from Diabetes Development in Nonobese Diabetic Mice by Generation of Tolerogenic APCs. *J. Immunol.* 195, 4176–4184. doi: 10.4049/jimmunol.1500884

Huppertz, B. (2008). Placental origins of preeclampsia: challenging the current hypothesis. *Hypertension* 51, 970–975. doi: 10.1161/HYPERTENSIONAHA.107.107607

Hutcheon, J. A., Lisonkova, S., and Joseph, K. S. (2011). Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. *Best Pract. Res. Clin. Obstet. Gynaecol.* 25, 391–403. doi: 10.1016j.bpobgyn.2011.01.006

Ilekis, J. V., Tsilou, E., Fisher, S., Abrahams, V. M., Soares, M. J., Cross, J. C., et al. (2016). Placental origins of adverse pregnancy outcomes: potential molecular targets: an Executive Workshop Summary of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. *Am. J. Obstet. Gynecol.* 215, S1–S46. doi: 10.1016/j.ajog.2016.03.001

Jakobsson, H. E., Abrahamsson, T. R., Jenmalm, M. C., Harris, K., Quince, C., Jernberg, C., et al. (2014). Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut* 63, 559–566. doi: 10.1136/gutjnl-2012-303249

Jimenez, E., Marin, M. L., Martin, R., Odriozola, J. M., Olivares, M., Xaus, J., et al. (2008). Is meconium from healthy newborns actually sterile? *Res. Microbiol.* 159, 187–193. doi: 10.1016/j.resmic.2007.12.007

Jin, M., Li, D., Ji, R., Liu, W., Xu, X., and Li, Y. (2019). Changes in intestinal microflora in digestive tract diseases during pregnancy. *Arch. Gynecol. Obstet.* doi: 10.1007/s00404-019-05336-0

Josefsdottir, K. S., Baldridge, M. T., Kadmon, C. S., and King, K. Y. (2017). Antibiotics impair murine hematopoiesis by depleting the intestinal microbiota. *Blood* 129, 729–739. doi: 10.1182/blood-2016-03-708594

Kalliomaki, M., Collado, M. C., Salminen, S., and Isolauri, E. (2008). Early differences in fecal microbiota composition in children may predict overweight. *Am. J. Clin. Nutr.* 87, 534–538. doi: 10.1093/ajcn/87.3.534

Kawai, T., and Akira, S. (2011). Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. *Immunity* 34, 637–650. doi: 10.1016/j.immuni.2011.05.006

Kell, D. B., and Kenny, L. C. (2016). A Dormant Microbial Component in the Development of Preeclampsia. *Front. Med. (Lausanne)* 3, 60. doi: 10.3389/fmed.2016.00060

Khan, M. J., Gerasimidis, K., Edwards, C. A., and Shaikh, M. G. (2016). Role of Gut Microbiota in the Aetiology of Obesity: Proposed Mechanisms and Review of the Literature. *J. Obes.* 2016, 7353642. doi: 10.1155/2016/7353642

Khan, I., Yasir, M., Farman, M., Kumosani, T., AlBasri, S. F., Bajouh, O. S., et al. (2019). Evaluation of gut bacterial community composition and antimicrobial resistome in pregnant and non-pregnant women from Saudi population. *Infect. Drug Resist.* 12, 1749–1761. doi: 10.2147/IDR.S200213

Kuang, Y. S., Lu, J. H., Li, S. H., Li, J. H., Yuan, M. Y., He, J. R., et al. (2017). Connections between the human gut microbiome and gestational diabetes mellitus. *Gigascience* 6, 1–12. doi: 10.1093/gigascience/gix058

Kumar, P., and Magon, N. (2012). Hormones in pregnancy. *Niger. Med. J.* 53, 179–183. doi: 10.4103/0300-1652.107549

Kumar, H., Lund, R., Laiho, A., Lundelin, K., Ley, R. E., Isolauri, E., et al. (2014). Gut microbiota as an epigenetic regulator: pilot study based on whole-genome methylation analysis. *mBio* 5. doi: 10.1128/mBio.02113-14

Lauenborg, J., Hansen, T., Jensen, D. M., Vestergaard, H., Molsted-Pedersen, L., Hornnes, P., et al. (2004). Increasing incidence of diabetes after gestational diabetes: a long-term follow-up in a Danish population. *Diabetes Care* 27, 1194–1199. doi: 10.2337/diacare.27.5.1194

Lezutekong, J. N., Nikhanj, A., and Oudit, G. Y. (2018). Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in cardiovascular disease. *Clin. Sci. (Lond)* 132, 901–904. doi: 10.1042/CS20180172

Lozupone, C. A., Stombaugh, J. I., Gordon, J. I., Jansson, J. K., and Knight, R. (2012). Diversity, stability and resilience of the human gut microbiota. *Nature* 489, 220–230. doi: 10.1038/nature11550

Luczynski, P., Tramullas, M., Viola, M., Shanahan, F., Clarke, G., O'Mahony, S., et al. (2017). Microbiota regulates visceral pain in the mouse. *Elife* 6. doi: 10.7554/eLife.25887

Luo, X. M., Edwards, M. R., Mu, Q., Yu, Y., Vieson, M. D., Reilly, C. M., et al. (2018). Gut Microbiota in Human Systemic Lupus Erythematosus and a Mouse Model of Lupus. *Appl. Environ. Microbiol.* 84. doi: 10.1128/AEM.02288-17

Lv, L. J., Li, S. H., Li, S. C., Zhong, Z. C., Duan, H. L., Tian, C., et al. (2019). Early-Onset Preeclampsia Is Associated With Gut Microbial Alterations in Antepartum and Postpartum Women. *Front. Cell Infect. Microbiol.* 9, 224. doi: 10.3389/fcimb.2019.00224

Mackie, R. I., Sghir, A., and Gaskins, H. R. (1999). Developmental microbial ecology of the neonatal gastrointestinal tract. *Am. J. Clin. Nutr.* 69, 1035S–1045S. doi: 10.1093/ajcn/69.5.1035s

Manfredo Vieira, S., Hiltensperger, M., Kumar, V., Zegarra-Ruiz, D., Dehner, C., Khan, N., et al. (2018). Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science* 359, 1156–1161. doi: 10.1126/science.aar7201

Matcovitch-Natan, O., Winter, D. R., Giladi, A., Vargas Aguilar, S., Spinrad, A., Sarrazin, S., et al. (2016). Microglia development follows a stepwise program to regulate brain homeostasis. *Science* 353, aad8670. doi: 10.1126/science.aad8670

Matthews, A., Haas, D. M., O'Mathuna, D. P., and Dowswell, T. (2015). Interventions for nausea and vomiting in early pregnancy. *Cochrane Database Syst. Rev.*, CD007575. doi: 10.1002/14651858.CD007575.pub4

McCann, A., Ryan, F. J., Stockdale, S. R., Dalmasso, M., Blake, T., Ryan, C. A., et al. (2018). Viromes of one year old infants reveal the impact of birth mode on microbiome diversity. *PeerJ* 6, e4694. doi: 10.7717/peerj.4694

McCarthy, F. P., Lutomski, J. E., and Greene, R. A. (2014). Hyperemesis gravidarum: current perspectives. *Int. J. Womens Health* 6, 719–725. doi: 10.1128/AEM.02288-17

Mol, B. W. J., Roberts, C. T., Thangaratinam, S., Magee, L. A., de Groot, C. J. M., and Hofmeyr, G. J. (2016). Pre-eclampsia. *Lancet* 387, 999–1011. doi: 10.1016/S0140-6736(15)00070-7

Mu, Q., Zhang, H., and Luo, X. M. (2015). SLE: Another Autoimmune Disorder Influenced by Microbes and Diet? *Front. Immunol.* 6, 608. doi: 10.3389/fimmu.2015.00608

Mu, Q., Tavella, V. J., Kirby, J. L., Cecere, T. E., Chung, M., Lee, J., et al. (2017a). Antibiotics ameliorate lupus-like symptoms in mice. *Sci. Rep.* 7, 13675. doi: 10.1038/s41598-017-14223-0

Mu, Q., Zhang, H., Liao, X., Lin, K., Liu, H., Edwards, M. R., et al. (2017b). Control of lupus nephritis by changes of gut microbiota. *Microbiome* 5, 73. doi: 10.1186/s40168-017-0300-8

Mu, Q., Cabana-Puig, X., Mao, J., Swartwout, B., Abdelhamid, L., Cecere, T. E., et al. (2019). Pregnancy and lactation interfere with the response of autoimmunity to modulation of gut microbiota. *Microbiome* 7, 105. doi: 10.1186/s40168-019-0720-8

Nakamura, Y., Franchi, L., Kambe, N., Meng, G., Strober, W., and Nunez, G. (2012). Critical role for mast cells in interleukin-1beta-driven skin inflammation associated with an activating mutation in the nlrp3 protein. *Immunity* 37, 85–95. doi: 10.1016/j.immuni.2012.04.013

Navab-Moghadam, F., Sedighi, M., Khamseh, M. E., Alaei-Shahmiri, F., Talebi, M., Razavi, S., et al. (2017). The association of type II diabetes with gut microbiota composition. *Microb. Pathog.* 110, 630–636. doi: 10.1016/j.micpath.2017.07.034

Nuriel-Ohayon, M., Neuman, H., and Koren, O. (2016). Microbial Changes during Pregnancy, Birth, and Infancy. *Front. Microbiol.* 7, 1031. doi: 10.3389/fmicb.2016.01031

Nyangahu, D. D., Lennard, K. S., Brown, B. P., Darby, M. G., Wendoh, J. M., Havyarimana, E., et al. (2018). Disruption of maternal gut microbiota during gestation alters offspring microbiota and immunity. *Microbiome* 6, 124. doi: 10.1186/s40168-018-0511-7

Odibo, A. O., Goetzinger, K. R., Odibo, L., and Tuuli, M. G. (2015). Early prediction and aspirin for prevention of pre-eclampsia (EPAPP) study: a randomized controlled trial. *Ultrasound Obstet. Gynecol.* 46, 414–418. doi: 10.1002/uog.14889

Ortqvist, A. K., Lundholm, C., Halfvarson, J., Ludvigsson, J. F., and Almqvist, C. (2019). Fetal and early life antibiotics exposure and very early onset inflammatory bowel disease: a population-based study. *Gut* 68, 218–225. doi: 10.1136/gutjnl-2017-314352

Pan, H., Guo, R., Ju, Y., Wang, Q., Zhu, J., Xie, Y., et al. (2019). A single bacterium restores the microbiome dysbiosis to protect bones from destruction in a rat model of rheumatoid arthritis. *Microbiome* 7, 107. doi: 10.1186/s40168-019-0719-1

Pannaraj, P. S., Li, F., Cerini, C., Bender, J. M., Yang, S., Rollie, A., et al. (2017). Association Between Breast Milk Bacterial Communities and Establishment and Development of the Infant Gut Microbiome. *JAMA Pediatr.* 171, 647–654. doi: 10.1001/jamapediatrics.2017.0378

Pedersen, H. K., Gudmundsdottir, V., Nielsen, H. B., Hyotylainen, T., Nielsen, T., Jensen, B. A., et al. (2016). Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature* 535, 376–381. doi: 10.1038/nature18646

Pelzer, E., Gomez-Arango, L. F., Barrett, H. L., and Nitert, M. D. (2017). Review: Maternal health and the placental microbiome. *Placenta* 54, 30–37. doi: 10.1016/j.placenta.2016.12.003

Poston, L., Caleyachetty, R., Cnattingius, S., Corvalan, C., Uauy, R., Herring, S., et al. (2016). Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes Endocrinol.* 4, 1025–1036. doi: 10.1016/S2213-8587(16)30217-0

Pronovost, G. N., and Hsiao, E. Y. (2019). Perinatal Interactions between the Microbiome, Immunity, and Neurodevelopment. *Immunity* 50, 18–36. doi: 10.1016/j.immuni.2018.11.016

Ricklin, D., Reis, E. S., and Lambris, J. D. (2016). Complement in disease: a defence system turning offensive. *Nat. Rev. Nephrol.* 12, 383–401. doi: 10.1038/nrneph.2016.70

Rothschild, D., Weissbrod, O., Barkan, E., Kurilshikov, A., Korem, T., Zeevi, D., et al. (2018). Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555, 210–215. doi: 10.1038/nature25973

Sacks, D. A., Hadden, D. R., Maresh, M., Deerochanawong, C., Dyer, A. R., Metzger, B. E., et al. (2012). Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care* 35, 526–528. doi: 10.2337/dc11-1641

Salmani, D., Purushothaman, S., Somashekara, S. C., Gnanagurudasan, E., Sumangaladevi, K., Harikishan, R., et al. (2014). Study of structural changes in placenta in pregnancy-induced hypertension. *J. Nat. Sci. Biol. Med.* 5, 352–355. doi: 10.4103/0976-9668.136182

Santacruz, A., Collado, M. C., Garcia-Valdes, L., Segura, M. T., Martin-Lagos, J. A., Anjos, T., et al. (2010). Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br. J. Nutr.* 104, 83–92. doi: 10.1017/S0007114510000176

Sanz, Y. (2011). Gut microbiota and probiotics in maternal and infant health. *Am. J. Clin. Nutr.* 94, 2000S–2005S. doi: 10.3945/ajcn.110.001172

Schneider, S., Hoeft, B., Freerksen, N., Fischer, B., Roehrig, S., Yamamoto, S., et al. (2011). Neonatal complications and risk factors among women with gestational diabetes mellitus. *Acta Obstet. Gynecol. Scand.* 90, 231–237. doi: 10.1111/j.1600-0412.2010.01040.x

Sekar, A., Bialas, A. R., de Rivera, H., Davis, A., Hammond, T. R., Kamitaki, N., et al. (2016). Schizophrenia risk from complex variation of complement component 4. *Nature* 530, 177–183. doi: 10.1038/nature16549

Smid, M. C., Ricks, N. M., Panzer, A., McCoy, A. N., Azcarate-Peril, M. A., Keku, T. O., et al. (2018). Maternal Gut Microbiome Biodiversity in Pregnancy. *Am. J. Perinatol.* 35, 24–30. doi: 10.1055/s-0037-1604412

Soderborg, T. K., Borengasser, S. J., Barbour, L. A., and Friedman, J. E. (2016). Microbial transmission from mothers with obesity or diabetes to infants: an innovative opportunity to interrupt a vicious cycle. *Diabetologia* 59, 895–906. doi: 10.1007/s00125-016-3880-0

Stilling, R. M., Ryan, F. J., Hoban, A. E., Shanahan, F., Clarke, G., Claesson, M. J., et al. (2015). Microbes & neurodevelopment–Absence of microbiota during early life increases activity-related transcriptional pathways in the amygdala. *Brain Behav. Immun.* 50, 209–220. doi: 10.1016/j.bbi.2015.07.009

Swartwout, B., and Luo, X. M. (2018). Implications of Probiotics on the Maternal-Neonatal Interface: Gut Microbiota, Immunomodulation, and Autoimmunity. *Front. Immunol.* 9, 2840. doi: 10.3389/fimmu.2018.02840

Theis, K. R., Romero, R., Winters, A. D., Greenberg, J. M., Gomez-Lopez, N., Alhousseini, A., et al. (2019). Does the human placenta delivered at term have a microbiota? Results of cultivation, quantitative real-time PCR, 16S rRNA gene sequencing, and metagenomics. *Am. J. Obstet. Gynecol.* 220, 267 e261–267 e239. doi: 10.1016/j.ajog.2018.10.018

Thion, M. S., Low, D., Silvin, A., Chen, J., Grisel, P., Schulte-Schrepping, J., et al. (2018). Microbiome Influences Prenatal and Adult Microglia in a Sex-Specific Manner. *Cell* 172, 500–516 e516. doi: 10.1016/j.cell.2017.11.042

Tincani, A., Dall'Ara, F., Lazzaroni, M. G., Reggia, R., and Andreoli, L. (2016). Pregnancy in patients with autoimmune disease: A reality in 2016. *Autoimmun. Rev.* 15, 975–977. doi: 10.1016/j.autrev.2016.07.017

Torres, J., Hu, J., Seki, A., Eisele, C., Nair, N., Huang, R., et al. (2020). Infants born to mothers with IBD present with altered gut microbiome that transfers abnormalities of the adaptive immune system to germ-free mice. *Gut* 69, 42–51. doi: 10.1136/gutjnl-2018-317855

Tsao, N. W., Hanley, G. E., Lynd, L. D., Amiri, N., and De Vera, M. A. (2019). Risk of congenital anomalies in infants born to women with autoimmune disease using biologics before or during pregnancy: a population-based cohort study. *Clin. Exp. Rheumatol.* 37, 976–982.

Vohr, B. R., and Boney, C. M. (2008). Gestational diabetes: the forerunner for the development of maternal and childhood obesity and metabolic syndrome? *J. Mater. Fetal. Neonatal. Med.* 21, 149–157. doi: 10.1080/14767050801929430

Vrieze, A., Holleman, F., Zoetendal, E. G., de Vos, W. M., Hoekstra, J. B., and Nieuwdorp, M. (2010). The environment within: how gut microbiota may influence metabolism and body composition. *Diabetologia* 53, 606–613. doi: 10.1007/s00125-010-1662-7

Vuong, H. E., and Hsiao, E. Y. (2017). Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. *Biol. Psychiatry* 81, 411–423. doi: 10.1016/j.biopsych.2016.08.024

Xie, R., Sun, Y., Wu, J., Huang, S., Jin, G., Guo, Z., et al. (2018). Maternal High Fat Diet Alters Gut Microbiota of Offspring and Exacerbates DSS-Induced Colitis in Adulthood. *Front. Immunol.* 9, 2608. doi: 10.3389/fimmu.2018.02608

Yan, F., Liu, L., Cao, H., Moore, D. J., Washington, M. K., Wang, B., et al. (2017). Neonatal colonization of mice with LGG promotes intestinal development and decreases susceptibility to colitis in adulthood. *Mucosal. Immunol.* 10, 117–127. doi: 10.1038/mi.2016.43

Yao, Y., Yu, H., Liu, Y., Xu, Q., Li, X., Meng, X., et al. (2018). PSTPIP2 Inhibits the Inflammatory Response and Proliferation of Fibroblast-Like Synoviocytes in vitro. *Front. Pharmacol.* 9, 1432. doi: 10.3389/fphar.2018.01432

Yao, Y., Cai, X., Yu, H., Xu, Q., Li, X., Yang, Y., et al. (2019). PSTPIP2 attenuates joint damage and suppresses inflammation in adjuvant-induced arthritis. *Eur. J. Pharmacol.* 859, 172558. doi: 10.1016/j.ejphar.2019.172558

Zambrano, E., Ibanez, C., Martinez-Samayoa, P. M., Lomas-Soria, C., Durand-Carbajal, M., and Rodriguez-Gonzalez, G. L. (2016). Maternal Obesity: Lifelong Metabolic Outcomes for Offspring from Poor Developmental Trajectories During the Perinatal Period. *Arch. Med. Res.* 47, 1–12. doi: 10.1016/j.arcmed.2016.01.004

Zhang, H., Liao, X., Sparks, J. B., and Luo, X. M. (2014). Dynamics of gut microbiota in autoimmune lupus. *Appl. Environ. Microbiol.* 80, 7551–7560. doi: 10.1128/AEM.02676-14

Zhang, Z., Chen, X., Zhao, J., Tian, C., Wei, X., Li, H., et al. (2019). Effects of a Lactulose-Rich Diet on Fecal Microbiome and Metabolome in Pregnant Mice. *J. Agric. Food Chem.* 67, 7674–7683. doi: 10.1021/acs.jafc.9b01479

Zhao, L., Zhang, F., Ding, X., Wu, G., Lam, Y. Y., Wang, X., et al. (2018). Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science* 359, 1151–1156. doi: 10.1126/science.aao5774

Zhou, L., and Xiao, X. (2018). The role of gut microbiota in the effects of maternal obesity during pregnancy on offspring metabolism. *Biosci. Rep.* 38. doi: 10.1042/BSR20171234

Zhu, Y., and Zhang, C. (2016). Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. *Curr. Diabetes Rep.* 16, 7. doi: 10.1007/s11892-015-0699-x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

MINI REVIEW
published: 02 October 2020
doi: 10.3389/fphar.2020.583354

Treatment of Autoimmune Bullous Diseases During Pregnancy and Lactation: A Review Focusing on Pemphigus and Pemphigoid Gestationis

Giovanni Genovese[1,2], *Federica Derlino*[3], *Emilio Berti*[1,2] *and Angelo Valerio Marzano*[1,2]*

[1] Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [2] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy, [3] Dermatology Unit, ASST Santi Paolo e Carlo, Milan, Italy

Pregnancy may induce the onset or exacerbation of autoimmune bullous diseases such as pemphigus or pemphigoid gestationis. A shift toward T helper (Th) 2 immune response and the influence of hormonal changes have been evoked as possible triggering factors. Therapeutic management of this setting of patients may represent a challenge, mainly due to safety concerns of some immunosuppressive drugs during pregnancy and lactation. In this narrative review, we provided a comprehensive overview of the therapeutic management of autoimmune bullous diseases in pregnant and breastfeeding women, focusing on pemphigus and pemphigoid gestationis.

Keywords: autoimmune bullous diseases, pemphigus, pregnancy, lactation, management, treatment

OPEN ACCESS

Edited by:
Cecilia Beatrice Chighizola, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Aurora Parodi, University of Genoa, Italy
Gabriele Simonini, University of Florence, Italy

***Correspondence:**
Angelo Valerio Marzano
angelo.marzano@unimi.it

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *14 July 2020*
Accepted: *15 September 2020*
Published: *02 October 2020*

Citation:
Genovese G, Derlino F, Berti E and Marzano AV (2020) Treatment of Autoimmune Bullous Diseases During Pregnancy and Lactation: A Review Focusing on Pemphigus and Pemphigoid Gestationis. Front. Pharmacol. 11:583354. doi: 10.3389/fphar.2020.583354

INTRODUCTION

Autoimmune bullous diseases (AIBDs) represent a group of mucocutaneous disorders that encompass different conditions hallmarked by autoreactive antibodies directed against epithelial adhesion molecules (Egami et al., 2020). Based on the localization of the blister, AIBDs are distinguished into two different categories: (i) AIBDs with intraepithelial cleavage, which belong to the pemphigus group (Kridin, 2018), including pemphigus vulgaris (PV) and pemphigus foliaceus (PF), and (ii) AIBDs with subepithelial detachment, which comprise diseases of the pemphigoid group (Amber et al., 2018) such as bullous pemphigoid (BP), pemphigoid gestationis (PG), mucous membrane pemphigoid (MMP), linear IgA bullous dermatosis (LABD), and epidermolysis bullosa acquisita (EBA). Among all these entities, PG and PV are those which involve more commonly women of childbearing potential (Feliciani et al., 2019). In particular, PG is regarded as a genuine specific dermatosis of pregnancy (Beard and Millington, 2012). On the other hand, PV and PF tend to occur frequently in young females and pregnancy may induce the onset or exacerbation of these diseases (Zhao and Murrell, 2015). Indeed, a shift toward T helper (Th) 2 immune response and the influence of hormonal changes have been indicated as possible triggering factors of AIBDs during pregnancy (Feliciani et al., 2019). Given that neonatal health is closely linked to the control of the underlying maternal AIBD, the issues related to the management of these disorders during pregnancy and lactation take on remarkable importance, often requiring a close interaction

among dermatologists, obstetricians and pediatricians. Furthermore, the unsafety during pregnancy or breastfeeding period of several immunosuppressive agents used to treat AIBD poses a major therapeutic challenge in this peculiar setting of patients (Kushner et al., 2018). On the other hand, achieving disease control can be hindered by pregnancy-associated hormonal changes and pregnancy complications (pre-eclampsia, gestational diabetes, intrauterine growth restrictions, and preterm birth). Both in pemphigus and PG, maternal autoantibodies can be transferred to the newborn determining the occurrence of neonatal blistering lesions. Neonatal disease usually resolves spontaneously within 1–4 weeks and, only in rare cases with widespread blisters, oral corticosteroids can be used to control the disease (Tavakolpour et al., 2017). Finally, randomized controlled trials on therapeutic options for AIBD in pregnancy are lacking due to the impossibility to perform them in this subset of patients.

In this narrative review, we have striven to provide a comprehensive overview of the management of AIBDs during pregnancy and lactation, focusing on pemphigus and PG, merging our experience with data extrapolated by case series and reviews.

TREATMENT OF PEMPHIGUS DURING PREGNANCY

Both PV and PF may appear for the first time (Kokolios et al., 2017) or relapse (Green and Maize, 1982) during pregnancy, showing the same clinical features observed in other subsets of patients (**Figures 1A, B**). In both cases, pregnancy needs to be classified as "high-risk" and the severity of the maternal disease requires to be controlled with safe agents and close monitoring of both mother and fetus. The same applies for patients who plan breastfeeding (Kardos et al., 2009). Women of childbearing age affected by pemphigus should be advised to avoid conception if they are on therapy with methotrexate, cyclophosphamide or mycophenolate mofetil. If on treatment with these drugs, they must be stopped and replaced. It is worth noting that pemphigus treatment in pregnant women is aimed at preventing both neonatal pemphigus (Zhao et al., 2016) and adverse pregnancy outcome such as preterm birth, low birth weight pre-eclampsia, stillbirth, and spontaneous abortion (Kardos et al., 2009). **Figure 2** shows a management algorithm based on current evidence (Kushner et al., 2018) and our experience for patients with pemphigus who plan conception or pregnant women who experience pemphigus onset, flare or poor response to treatment. Immunosuppressive treatments commonly used to treat pemphigus such as mycophenolate mofetil (Food and Drug Administration [FDA] pregnancy category D), cyclophosphamide (FDA pregnancy category D), and methotrexate (FDA pregnancy category X) have been contraindicated during pregnancy by the most representative Societies of Rheumatology (Flint et al., 2016; Götestam Skorpen et al., 2016; Sammaritano et al., 2020) and Gynecology (Committee on Obstetric Practice Society for Maternal-Fetal Medicine, 2019). The use of tetracyclines, which have been reported to be effective in some cases of pemphigus (Hone and Mutasim, 2016), is also discouraged by the FDA due to

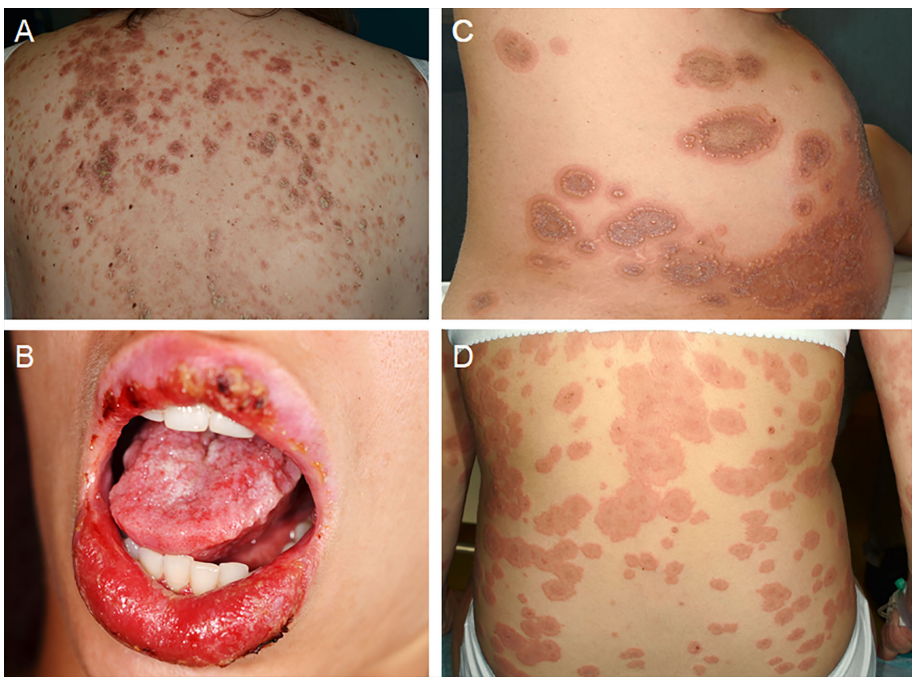


FIGURE 1 | Clinical features of autoimmune bullous diseases during pregnancy. **(A)** Erythematous-scaling lesions on the back of a pregnant patient with pemphigus foliaceus. **(B)** Oral erosions in a pregnant patient with pemphigus vulgaris. **(C, D)** Urticarial plaques associated with vesiculobullous lesions in two pregnant patients with pemphigoid gestationis. Written informed consent was obtained from all patients for the publication of clinical images.

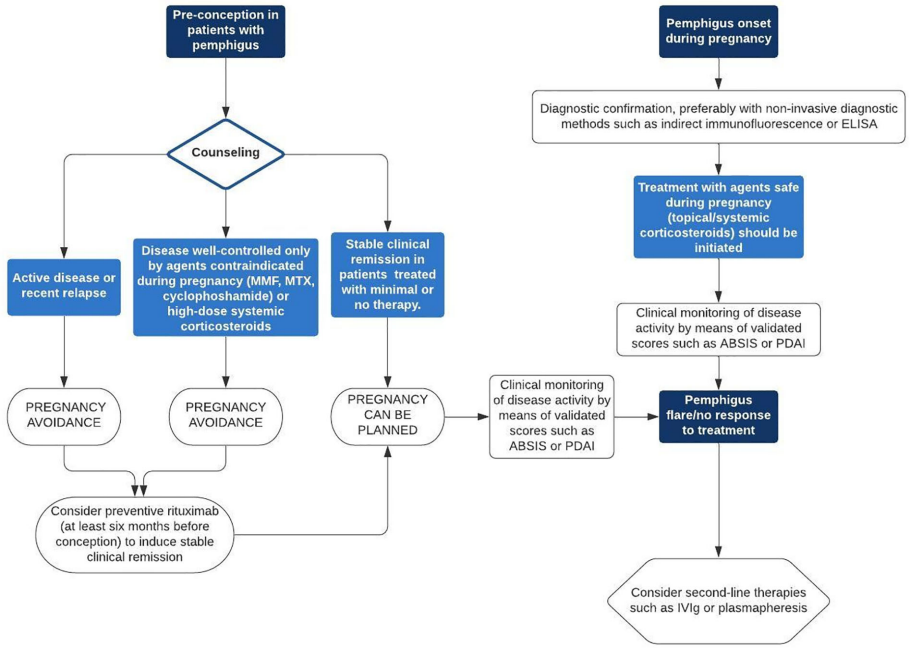


FIGURE 2 | Management algorithm for patients with pemphigus who plan conception or pregnant women who experience pemphigus onset, flare or poor response to treatment. ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; ELISA, enzyme-linked immunosorbent assay; IVIg, intravenous immunoglobulin therapy; MMF, mycophenolate mofetil; MTX, methotrexate; PDAI, Pemphigus Disease Area Index.

their teratogenicity and bone growth disruption (Kushner et al., 2018). Data on azathioprine (FDA pregnancy category D) safety during pregnancy are controversial (Patsatsi et al., 2019). Even if it some initial studies reported increased risk of congenital defects in babies born from mother treated with azathioprine (Nørgård et al., 2003), more recent evidence seem to suggest that no association between fetal exposure to azathioprine during pregnancy and birth defects (Goldstein et al., 2007) or other adverse pregnancy outcomes such as low birth weight (Akbari et al., 2013) exist. The 2020 guidelines and recommendations endorsed by the American College of Rheumatology recommend azathioprine as compatible for use throughout pregnancy (Sammaritano et al., 2020).

Women treated with mycophenolate mofetil, methotrexate or cyclophosphamide should be advised to discontinue therapy 6 weeks, 3 months and one ovulation cycle before conception, respectively (Patsatsi et al., 2019). The authors of a very recent systematic review on the effect of paternal exposure to immunosuppressive drugs on fertility, pregnancy and offspring outcomes concluded that data regarding pregnancy and offspring outcomes were limited but no significant negative effects associated with paternal immunosuppressant exposure were reported (Perez-Garcia et al., 2020).

TREATMENT OF PEMPHIGOID GESTATIONIS

PG is a subepithelial autoimmune blistering disease associated with pregnancy, puerperium, or, more rarely, gestational trophoblastic disease (**Figures 1C, D**) (Ambros-Rudolph et al., 2006). Although it usually resolves after delivery, it may also show a persistent or chronic-relapsing course, with flares usually occurring after delivery, during menses, or in association with the use of hormonal contraceptives. In cases associated with gestational trophoblastic disease, the treatment of underlying condition may facilitate PG remission (Slazinski and Degefu, 1982; do Valle Chiossi et al., 2000; Djahansouzi et al., 2003). The treatment is non-standardized, with most evidence derived from individual case reports or small series, currently there being no specific guidelines. In our experience, high-potency topical corticosteroids as monotherapy can be used in mild cases, while systemic corticosteroids (prednisone 0.5 mg/kg/day) should be reserved for moderate-to-severe cases. In case of inadequate response, it is reasonable to increase the dosage of systemic corticosteroids or consider adding/replacing systemic corticosteroids with a steroid-sparing agent (e.g., dapsone or intravenous immunoglobulin therapy [IVIg]).

THERAPEUTIC OPTIONS FOR PEMPHIGUS AND PEMPHIGOID GESTATIONIS DURING PREGNANCY

Systemic Corticosteroids (FDA Pregnancy Category C)

In pregnant patients with pemphigus, systemic corticosteroids alone or in combination with topical corticosteroids or steroid-

sparing agents such as azathioprine or IVIg, are the mainstay of treatment, as suggested also by the case series of Daneshpazooh et al. (2011) and in the reviews by Lin et al. (2015) and Kardos et al. (2009). The good safety profile during pregnancy and lactation and the effectiveness of these agents make low-dosage (less than 20 mg/day) (Murase et al., 2014) systemic corticosteroids a first-line therapeutic option in this setting. Systemic corticosteroids, sometimes combined with topical corticosteroids, seem to be the mainstay also for PG treatment, particularly during pregnancy and in mild-to-moderate cases (Piva et al., 2014; Veiga et al., 2018).

Topical Corticosteroids (FDA Pregnancy Category C)

Topical corticosteroids may represent a first-line treatment in patients with stable pemphigus, either as monotherapy (Moncada et al., 1982; Chowdhury and Natarajan, 1998; Çayırlı et al., 2015) in mild disease or in combination with systemic corticosteroids in more severe cases (Hern et al., 1998). Although they have been demonstrated to be not associated with severe adverse pregnancy outcome (Chi et al., 2016), very potent topical corticosteroids may cause fetal growth restrictions. This is due to a systemic absorption, most encountered when used on the skin of eyelids, genitals and folds. Successful treatment with topical corticosteroids as monotherapy has also been reported in PG, particularly for mild or localized skin lesions during pregnancy but also after delivery, for mild relapses (e.g., during menses) (Cozzani et al., 2005; Fukuda et al., 2012; Ingen-Housz-Oro et al., 2016).

Topical Calcineurin Inhibitors (FDA Pregnancy Category C)

Topical tacrolimus and pimecrolimus are poorly absorbed systemically because their molecular size prevents skin penetration. For this reason, although there are no controlled trials on topical calcineurin inhibitors in pregnant women with AIBDs, it has been suggested that, when no alternatives exist, their use on small areas is admissible (Murase et al., 2014).

Dapsone (FDA Pregnancy Category C)

Dapsone is an antibiotic belonging to the class of sulphones recommended for the treatment of leprosy. Owing to its antinflammatory properties, it is widely used by dermatologists in different skin diseases, including AIBDs (Kushner et al., 2018). It is a safe option in pregnant patients without glucose-6-phosphate dehydrogenase (G6PDH) deficiency and can be used during lactation monitoring the baby for hemolysis and G6PDH deficiency (Kushner et al., 2018). Data on its use for treating pemphigus during pregnancy are limited. To our knowledge, there is only one report in the literature describing the use of dapsone for treating PV during pregnancy, leading to disease control. However, in the same report, a stillborn likely not related to dapsone use was recorded (Terpstra et al., 1979). Dapsone as monotherapy (Tani et al., 2015) or in combination with systemic corticosteroids (Kirtschig et al., 1994; Soares et al., 2018) may be a good option in patients with PG showing a tendency to persist after delivery.

Rituximab (FDA Pregnancy Category C)

Rituximab is a chimeric, humanized anti-CD20 monoclonal antibody exerting its effects in pemphigus through depletion of B cells, which are responsible for the production of anti-desmoglein autoantibodies.

Although current evidence indicates no increased rate of congenital malformations (Ojeda-Uribe et al., 2013; Sangle et al., 2013), rituximab may cross the transplacental barriers, particularly in the third trimester, and its use in fertile women should take into consideration the risk of fetal lymphocyte B depletion (Klink et al., 2008; Chakravarty et al., 2011). Furthermore, it is possible that rituximab is associated with prematurity and spontaneous abortion (Chakravarty et al., 2011). For these reasons, women are advised to try to conceive at least 12 months after the last rituximab administration (Kushner et al., 2018). However, recent reports (Lake et al., 2017; Vassallo et al., 2017) emphasized that clinical remission of pemphigus may be achieved using rituximab in the pre-conception period, allowing to discontinue immunosuppressive drugs contraindicated in pregnancy. Interestingly, rituximab has been successfully used either after delivery for treating a recalcitrant PG case (Cianchini et al., 2007) and during pregnancy for preventing PG relapse (Tourte et al., 2017).

Intravenous Immunoglobulin Therapy (FDA Pregnancy Category C)

IVIg is a therapeutic option used for treating pemphigus patients with inadequate response or intolerance to systemic corticosteroids or conventional immunosuppressants (Bystryn et al., 2002; Amagai et al., 2009). IVIg acts by blocking the Fc receptor on the surface of macrophages and inhibiting the autoantibody production (Tavakolpour et al., 2017). Its safety during pregnancy has been demonstrated also by studies conducted for a variety of antibody-mediated autoimmune diseases other than pemphigus (Perricone et al., 2008; Sun et al., 2016). In addition, IVIg does not increase the risk of infection and seem to reduce the risk of neonatal pemphigus (Ahmed and Gürcan, 2011). As proof of this, Ono et al. (2018) showed in an experimental study on mouse model that IVIg prevented the transplacental maternal-to-fetal autoantibody transfer. Despite the above-mentioned advantages, the high cost of IVIg relegate it to second-line treatment in pregnant patients with corticosteroid-unresponsive pemphigus (Tavakolpour et al., 2017). Bostan et al. (2020) recently reported on a patient with PV begun during pregnancy who was successfully treated with a combination of IVIg and systemic corticosteroids as first-line option. The most relevant study on this topic was published in 2011 by Ahmed and Gürcan (2011), who analyzed the outcomes of eight patients with active PV during pregnancy treated with IVIg at a dosage of 2 g/kg/cycle. They found that IVIg can be useful and safe in treating pregnant patients with PV also in early phases of pregnancy. In turn, IVIg represents a good option for PG during the gestational period either as monotherapy (Nguyen et al., 2015) or combined with systemic corticosteroids (Doiron and Pratt, 2010; De la Calle et al., 2017).

Plasmapheresis/Plasma Exchange

Plasmapheresis is a procedure consisting in removing plasma, which undergoes further processing to eliminate pathological substances such as autoantibodies, and then is returned (Reeves and Winters, 2014). In plasma exchange, the removed plasma is discarded and replaced with either a colloid solution or a combination of crystalloid and colloid solutions (Reeves and Winters, 2014). These procedures are used as an alternative therapeutic option for severe or refractory pemphigus (Nagasaka et al., 2008). Plasmapheresis and plasma exchange are considered to be a safe procedure during pregnancy, and a number of authors reported on cases of PV successfully treated with plasmapheresis/plasma exchange during pregnancy (Piontek et al., 2000; Shieh et al., 2004; Gushi et al., 2008). Plasmapheresis/plasma exchange has been performed either in combination with systemic corticosteroids (Patsatsi et al., 2012) or as monotherapy also for PG (Van de Wiel et al., 1980).

Tumour Necrosis Factor α (TNF-α) Inhibitors

Although TNF-α has been suggested to play a role in inducing acantholysis in pemphigus, results on the effectiveness of TNF-α inhibitors, such as etanercept and infliximab, in AIBDs are conflicting (Jacobi et al., 2005; Fiorentino et al., 2011; Hall et al., 2015). However, the potential use of these drugs during pregnancy and mostly during breastfeeding needs always to be considered. A systematic review on pregnant patients with inflammatory bowel diseases revealed that the rate of adverse pregnancy outcome and malformation in patients treated with TNF-α antagonists is not significantly higher than expected in the general population (Nielsen et al., 2013). However, possible increased risk of neonatal infections has been suggested if these drugs are administered during the third trimester (Ostensen, 2014). The EULAR task force recommended continuation of TNF-α antagonists during the first part of pregnancy and suggested etanercept and certolizumab for use throughout pregnancy due to low rate of transplacental passage (Götestam Skorpen et al., 2016). No data are available for the treatment of PG with TNFα inhibitors to date.

TREATMENT OF AUTOIMMUNE BULLOUS DISEASES DURING LACTATION

Topical corticosteroids and topical calcineurin inhibitors are admitted during lactation unless they are applied in the nipple area before breastfeeding (Butler et al., 2014). In the same way, systemic corticosteroids are considered to be compatible with lactation, with the *caveat* that they should be administered at least 4 h before breastfeeding (Temprano et al., 2005). No active metabolites of mercaptopurine were detected in the blood of breastfed sons of mothers in treatment with azathioprine and no azathioprine-associated adverse effects have been observed (Angelberger et al., 2011). For these reasons, the American College of Rheumatology declared that azathioprine is conditionally recommended as compatible with breastfeeding (Birru Talabi and Clowse, 2020). However, caution should be exercised in thiopurine methyltransferase-deficient individuals (Götestam Skorpen et al., 2016) .While controlled trials are lacking, it is conceivable that IVIg is safe to be used during breastfeeding (Achiron et al., 2004). In a recent literature review, Götestam Skorpen et al. reported no adverse events in breastfed children of mothers on IVIg in most cases (n=146/149) and a transient rash only in a child (Götestam Skorpen et al., 2016). For these reasons, they are considered compatible with breastfeeding. (Götestam Skorpen et al., 2016) Plasmapheresis and immunoadsorption have been shown to be safe and well-tolerated in breastfeeding (Dittrich et al., 2002). Although rituximab has been recommended to be avoided during breastfeeding due to lack of data (Götestam Skorpen et al., 2016), it may be regarded as compatible with breastfeeding if no other options are available, since it is excreted in minimal amounts into human breast milk, likely owing to its large molecular size that impedes the transfer across the mammary tissues (Bragnes et al., 2017). TNFα antagonists, which are either minimally excreted in breast milk or scarcely absorbed, have been considered compatible with breastfeeding by the EULAR task force (Götestam Skorpen et al., 2016). Conversely, methotrexate, cyclophosphamide and mycophenolate are considered not compatible with lactation by the American College of Rheumatology and the British Society of Rheumatology due to the high risk of being transferred into breast milk (Birru Talabi and Clowse, 2020).

CONCLUSION

The role of pre-pregnancy counseling is of primary importance in patients affected by pemphigus who plan to become pregnant. The most relevant aim is to induce and maintain a stable disease remission. The minimum therapeutically effective dose should be administered during pregnancy in order to prevent disease flares, which are linked to adverse pregnancy outcomes. The treatment of both pemphigus and PG mainly relies on systemic corticosteroids. However, patients who are refractory or intolerant to these agents may be treated with steroid-sparing treatments, such as dapsone, IVIg, or plasmapheresis.

AUTHOR CONTRIBUTIONS

GG and AM designed and wrote the initial draft of the manuscript. FD and EB reviewed the paper and provided critical intellectual input. All authors contributed to the article and approved the submitted version.

REFERENCES

Achiron, A., Kishner, I., Dolev, M., Stern, Y., Dulitzky, M., Schiff, E., et al. (2004). Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis. *J. Neurol.* 251, 1133–1137. doi: 10.1007/s00415-004-0495-z

Ahmed, A. R., and Gürcan, H. M. (2011). Use of intravenous immunoglobulin therapy during pregnancy in patients with pemphigus vulgaris. *J. Eur. Acad. Dermatol. Venereol.* 25, 1073–1079. doi: 10.1111/j.1468-3083.2010.03925.x

Akbari, M., Shah, S., Velayos, F. S., Mahadevan, U., and Cheifetz, A. S. (2013). Systematic review and meta-analysis on the effects of thiopurines on birth outcomes from female and male patients with inflammatory bowel disease. *Inflammation Bowel Dis.* 19, 15–22. doi: 10.1002/ibd.22948

Amagai, M., Ikeda, S., Shimizu, H., Iizuka, H., Hanada, K., Aiba, S., et al. (2009). A randomized double-blind trial of intravenous immunoglobulin for pemphigus. *J. Am. Acad. Dermatol.* 60, 595–603. doi: 10.1016/j.jaad.2008.09.052

Amber, K. T., Murrell, D. F., Schmidt, E., Joly, P., and Borradori, L. (2018). Autoimmune Subepidermal Bullous Diseases of the Skin and Mucosae: Clinical Features, Diagnosis, and Management. *Clin. Rev. Allergy Immunol.* 54, 26–51. doi: 10.1007/s12016-017-8633-4

Ambros-Rudolph, C. M., Müllegger, R. R., Vaughan-Jones, S. A., Kerl, H., and Black, M. M. (2006). The specific dermatoses of pregnancy revisited and reclassified: results of a retrospective two-center study on 505 pregnant patients. *J. Am. Acad. Dermatol.* 54, 395–404. doi: 10.1016/j.jaad.2005.12.012

Angelberger, S., Reinisch, W., Messerschmidt, A., Miehsler, W., Novacek, G., Vogelsang, H., et al. (2011). Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. *J. Crohns Colitis* 5, 95–100. doi: 10.1016/j.crohns.2010.10.005

Beard, M. P., and Millington, G. W. (2012). Recent developments in the specific dermatoses of pregnancy. *Clin. Exp. Dermatol.* 37, 1–5. doi: 10.1111/j.1365-2230.2011.04173.x

Birru Talabi, M., and Clowse, M. E. B. (2020). Antirheumatic medications in pregnancy and breastfeeding. *Curr. Opin. Rheumatol.* 32, 238–246. doi: 10.1097/BOR.0000000000000710

Bostan, E., Gülseren, D., Ersoy Evans, S., Elçin, G., Karaduman, A., and Atakan, N. (2020). Efficacious treatment of pemphigus vulgaris by intravenous immunoglobulin during pregnancy and postpartum period. *Dermatol. Ther.* 33, e13187. doi: 10.1111/dth.13187

Bragnes, Y., Boshuizen, R., de Vries, A., Lexberg, Å., and Østensen, M. (2017). Low level of Rituximab in human breast milk in a patient treated during lactation. *Rheumatol. (Oxford)* 56, 1047–1048. doi: 10.1093/rheumatology/kex039

Butler, D. C., Heller, M. M., and Murase, J. E. (2014). Safety of dermatologic medications in pregnancy and lactation: Part II. Lactation. *J. Am. Acad. Dermatol.* 70, 417.e1–417427. doi: 10.1016/j.jaad.2013.09.009

Bystryn, J. C., Jiao, D., and Natow, S. (2002). Treatment of pemphigus with intravenous immunoglobulin. *J. Am. Acad. Dermatol.* 47, 358–363. doi: 10.1067/mjd.2002.122735

Çayırlı, M., Tunca, M., Akar, A., and Akpak, Y. K. (2015). Favourable outcome of pregnancy in a patient with pemphigus vulgaris. *J. Obstet. Gynaecol.* 35, 747–748. doi: 10.3109/01443615.2014.993939

Chakravarty, E. F., Murray, E. R., Kelman, A., and Farmer, P. (2011). Pregnancy outcomes after maternal exposure to rituximab. *Blood* 117 (5), 1499–1506. doi: 10.1182/blood-2010-07-295444

Chi, C. C., Wang, S. H., and Kirtschig, G. (2016). Safety of Topical Corticosteroids in Pregnancy. *JAMA Dermatol.* 152, 934–935. doi: 10.1001/jamadermatol.2016.1009

Chowdhury, M. M., and Natarajan, S. (1998). Neonatal pemphigus vulgaris associated with mild oral pemphigus vulgaris in the mother during pregnancy. *Br. J. Dermatol.* 139, 500–503. doi: 10.1046/j.1365-2133.1998.02418.x

Cianchini, G., Masini, C., Lupi, F., Corona, R., De Pità, O., and Puddu, P. (2007). Severe persistent pemphigoid gestationis: long-term remission with rituximab. *Br. J. Dermatol.* 157, 388–389. doi: 10.1111/j.1365-2133.2007.07982.x

Committee on Obstetric Practice Society for Maternal-Fetal Medicine (2019). Immune modulating therapies in pregnancy and lactation. ACOG Committee Opinion No. 776. American College of Obstetricians and Gynecologists. *Obstet. Gynecol.* 133, e287–e295. doi: 10.1097/AOG.0000000000003176

Cozzani, E., Basso, M., Parodi, A., and Rebora, A. (2005). Pemphigoid gestationis post partum after changing husband. *Int. J. Dermatol.* 44, 1057–1058. doi: 10.1111/j.1365-4632.2004.02548.x

Daneshpazhooh, M., Chams-Davatchi, C., Valikhani, M., Aghabagheri, A., Mortazavizadeh, S. M., Barzegari, M., et al. (2011). Pemphigus and pregnancy: a 23-year experience. *Indian J. Dermatol. Venereol. Leprol.* 77, 534. doi: 10.4103/0378-6323.82404

De la Calle, M., Vidaurrázaga, C., Martinez, N., González-Beato, M., Antolín, E., and Bartha, J. L. (2017). Successful treatment of a severe early onset case of pemphigoid gestationis with intravenous immunoglobulin in a twin pregnancy conceived with in vitro fertilisation in a primigravida. *J. Obstet. Gynaecol.* 37, 246–247. doi: 10.1080/01443615.2016.1244809

Dittrich, E., Schmaldienst, S., Langer, M., Jansen, M., Hörl, W. H., and Derfler, K. (2002). Immunoadsorption and plasma exchange in pregnancy. *Kidney Blood Press Res.* 25, 232–239. doi: 10.1159/000066343

Djahansouzi, S., Nestle-Kraemling, C., Dall, P., Bender, H. G., and Hanstein, B. (2003). Herpes gestationis may present itself as a paraneoplastic syndrome of choriocarcinoma-a case report. *Gynecol. Oncol.* 89, 334–337. doi: 10.1016/s0090-8258(03)00070-2

do Valle Chiossi, M. P., Costa, R. S., and Ferreira Roselino, A. M. (2000). Titration of herpes gestationis factor fixing to C3 in pemphigoid herpes gestationis associated with choriocarcinoma. *Arch. Dermatol.* 136, 129–130. doi: 10.1001/archderm.136.1.129-a

Doiron, P., and Pratt, M. (2010). Antepartum intravenous immunoglobulin therapy in refractory pemphigoid gestationis: case report and literature review. *J. Cutan. Med. Surg.* 14, 189–192. doi: 10.2310/7750.2009.09001

Egami, S., Yamagami, J., and Amagai, M. (2020). Autoimmune bullous skin diseases, pemphigus and pemphigoid. *J. Allergy Clin. Immunol.* 145, 1031–1047. doi: 10.1016/j.jaci.2020.02.013

Feliciani, C., Genovese, G., D'Astolto, R., Pontini, P., and Marzano, A. V. (2019). Autoimmune bullous diseases during pregnancy: insight into pathogenetic mechanisms and clinical features. *G. Ital. Dermatol. Venereol.* 154, 256–262. doi: 10.23736/S0392-0488.18.06153-9

Fiorentino, D. F., Garcia, M. S., Rehmus, W., and Kimball, A. B. (2011). A pilot study of etanercept treatment for pemphigus vulgaris. *Arch. Dermatol.* 147, 117–118. doi: 10.1001/archdermatol.2010.409

Flint, J., Panchal, S., Hurrell, A., van de Venne, M., Gayed, M., Schreiber, K., et al. (2016). BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatol. (Oxford)* 55, 1693–1697. doi: 10.1093/rheumatology/kev404

Fukuda, S., Ishii, N., Hamada, T., Ohyama, B., Momosaki, N., Karashima, T., et al. (2012). A case of herpes gestationis: follow-up study of autoantibodies using enzyme-linked immunosorbent assay and immunoblotting. *Indian J. Dermatol. Venereol. Leprol.* 78, 199–201. doi: 10.4103/0378-6323.93646

Goldstein, L. H., Dolinsky, G., Greenberg, R., Schaefer, C., Cohen-Kerem, R., Diav-Citrin, O., et al. (2007). Pregnancy outcome of women exposed to azathioprine during pregnancy. *Birth Defects Res. A. Clin. Mol. Teratol.* 79, 696–701. doi: 10.1002/bdra.20399

Götestam Skorpen, C., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., et al. (2016). The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheumatol. Dis.* 75, 795–810. doi: 10.1136/annrheumdis-2015-208840

Green, D., and Maize, J. C. (1982). Maternal pemphigus vulgaris with in vivo bound antibodies in the stillborn fetus. *J. Am. Acad. Dermatol.* 7, 388–392. doi: 10.1016/s0190-9622(82)70125-2

Gushi, M., Yamamoto, Y., Mine, Y., Awazawa, R., Nonaka, K., Taira, K., et al. (2008). Neonatal pemphigus vulgaris. *J. Dermatol.* 35, 529–535. doi: 10.1111/j.1346-8138.2008.00515.x

Hall, R. P., Fairley, J., Woodley, D., Werth, V. P., Hannah, D., Streilein, R. D., et al. (2015). A multicentre randomized trial of the treatment of patients with pemphigus vulgaris with infliximab and prednisone compared with prednisone alone. *Br. J. Dermatol.* 172, 760–768. doi: 10.1111/bjd.13350

Hern, S., Vaughan Jones, S. A., Setterfield, J., Du Peloux Menag, H., Greaves, M. W., Rowlatt, R., et al. (1998). Pemphigus vulgaris in pregnancy with favourable foetal prognosis. *Clin. Exp. Dermatol.* 23, 260–263. doi: 10.1046/j.1365-2230.1998.00370.x

Hone, N. L., and Mutasim, D. F. (2016). Pemphigus vulgaris successfully treated with doxycycline monotherapy. *Cutis* 97, E25–E27.

Ingen-Housz-Oro, S., Sbidian, E., Ortonne, N., Poirier, E., Chosidow, O., and Wolkenstein, P. (2016). Pemphigoid gestationis revealing a denial of pregnancy. *J. Eur. Acad. Dermatol. Venereol.* 30, 1411–1413. doi: 10.1111/jdv.13257

Jacobi, A., Shuler, G., and Hertl, M. (2005). Rapid control of therapy-refractory pemphigus vulgaris by treatment with the tumour necrosis factor-alpha inhibitor infliximab. *Br. J. Dermatol.* 153, 448–449. doi: 10.1111/j.1365-2133.2005.06744.x

Kardos, M., Levine, D., Gürcan, H. M., and Ahmed, R. A. (2009). Pemphigus vulgaris in pregnancy: analysis of current data on the management and outcomes. *Obstet. Gynecol. Surv.* 64, 739–749. doi: 10.1097/OGX.0b013e3181bea089

Kirtschig, G., Collier, P. M., Emmerson, R. W., and Wojnarowska, F. (1994). Severe case of pemphigoid gestationis with unusual target antigen. *Br. J. Dermatol.* 131, 108–111. doi: 10.1111/j.1365-2133.1994.tb08466.x

Klink, D. T., van Elburg, R. M., Schreurs, M. W., and van Well, G. T. (2008). Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. *Clin. Dev. Immunol.* 2008, 271363. doi: 10.1155/2008/271363

Kokolios, M., Lamprou, F., Stylianidou, D., Sotiriadis, D., and Patsatsi, A. (2017). New onset pemphigus foliaceus during pregnancy: A rare case. *Int. J. Womens. Dermatol.* 4, 109–112. doi: 10.1016/j.ijwd.2017.10.010

Kridin, K. (2018). Pemphigus group: overview, epidemiology, mortality, and comorbidities. *Immunol. Res.* 66, 255–270. doi: 10.1007/s12026-018-8986-7

Kushner, C. J., Concha, J. S. S., and Werth, V. P. (2018). Treatment of Autoimmune Bullous Disorders in Pregnancy. *Am. J. Clin. Dermatol.* 19, 391–403. doi: 10.1007/s40257-018-0342-0

Lake, E. P., Huang, Y. H., and Aronson, I. K. (2017). Rituximab treatment of pemphigus in women of childbearing age: experience with two patients. *J. Dermatol. Treat.* 28, 751–752. doi: 10.1080/09546634.2016.1255302

Lin, L., Zeng, X., and Chen, Q. (2015). Pemphigus and pregnancy. Analysis and summary of case reports over 49 years. *Saudi Med. J.* 36, 1033–1038. doi: 10.15537/smj.2015.9.12270

Moncada, B., Kettelsen, S., Hernández-Moctezuma, J. L., and Ramirez, F. (1982). Neonatal pemphigus vulgaris: role of passively transferred pemphigus antibodies. *Br. J. Dermatol.* 106, 465–467. doi: 10.1111/j.1365-2133.1982.tb04542.x

Murase, J. E., Heller, M. M., and Butler, D. C. (2014). Safety of dermatologic medications in pregnancy and lactation: Part I. *Pregnancy J. Am. Acad. Dermatol.* 70, 401.e1–401415. doi: 10.1016/j.jaad.2013.09.010

Nagasaka, T., Fujii, Y., Ishida, A., Handa, M., Tanikawa, A., Amagai, M., et al. (2008). Evaluating efficacy of plasmapheresis for patients with pemphigus using desmoglein enzyme-linked immunosorbent assay. *Br. J. Dermatol.* 158 (4), 685–690. doi: 10.1111/j.1365-2133.2007.08416.x

Nguyen, T., Alraqum, E., and Razzaque Ahmed, A. (2015). Positive clinical outcome with IVIg as monotherapy in recurrent pemphigoid gestationis. *Int. Immunopharmacol.* 26, 1–3. doi: 10.1016/j.intimp.2015.02.038

Nielsen, O. H., Loftus, E. V.Jr, and Jess, T. (2013). Safety of TNF-alpha inhibitors during IBD pregnancy: a systematic review. *BMC Med.* 11, 174. doi: 10.1186/1741-7015-11-174

Nørgård, B., Pedersen, L., Fonager, K., Rasmussen, S. N., and Sørensen, H. T. (2003). Azathioprine, mercaptopurine and birth outcome: a population-based cohort study. *Aliment Pharmacol. Ther.* 17, 827–834. doi: 10.1046/j.1365-2036.2003.01537.x

Ojeda-Uribe, M., Afif, N., Dahan, E., Sparsa, L., Haby, C., Sibilia, J., et al. (2013). Exposure to abatacept or rituximab in the first trimester of pregnancy in three women with autoimmune diseases. *Clin. Rheumatol.* 32, 695–700. doi: 10.1007/s10067-012-2156-4

Ono, S., Egawa, G., Honda, T., and Kabashima, K. (2018). Intravenous immunoglobulin treatment abrogates transplacental autoantibody transfer in a murine pemphigus model. *J. Allergy Clin. Immunol.* 141 (6), 2273–2276.e1. doi: 10.1016/j.jaci.2017.12.985

Ostensen, M. (2014). Safety issues of biologics in pregnant patients with rheumatic diseases. *Ann. N. Y. Acad. Sci.* 1317, 32–38. doi: 10.1111/nyas.12456

Patsatsi, A., Vavilis, D., Tsikeloudi, M., Kalabalikis, D., and Sotiriadis, D. (2012). Refractory pemphigoid gestationis postpartum. *Acta Obstet. Gynecol. Scand.* 91, 636–637. doi: 10.1111/j.1600-0412.2012.01379.x

Patsatsi, A., Marinovic, B., and Murrell, D. (2019). Autoimmune bullous diseases during pregnancy: Solving common and uncommon issues. *Int. J. Womens Dermatol.* 5, 166–170. doi: 10.1016/j.ijwd.2019.01.003

Perez-Garcia, L. F., Dolhain, R. J. E. M., Vorstenbosch, S., Bramer, W., van Puijenbroek, E., Hazes, J. M. W., et al. (2020). The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. *Hum. Reprod.* doi: 10.1093/humupd/dmaa022

Perricone, R., De Carolis, C., Kröegler, B., Greco, E., Giacomelli, R., Cipriani, P., et al. (2008). Intravenous immunoglobulin therapy in pregnant patients affected with systemic lupus erythematosus and recurrent spontaneous abortion. *Rheumatol. (Oxford)* 47, 646–651. doi: 10.1093/rheumatology/ken046

Piontek, J. O., Borberg, H., Sollberg, S., Krieg, T., and Hunzelmann, N. (2000). Severe exacerbation of pemphigus vulgaris in pregnancy: successful treatment with plasma exchange. *Br. J. Dermatol.* 143, 455–456. doi: 10.1046/j.1365-2133.2000.03686.x

Piva, I., Lo Monte, G., Graziano, A., and Marci, R. (2014). Herpes Gestationis after Ovodonation: Is Placenta the only Target of the Immune Reaction? *J. Clin. Diagn. Res.* 8, OD01–OOD2. doi: 10.7860/JCDR/2014/8727.5103

Reeves, H. M., and Winters, J. L. (2014). The mechanisms of action of plasma exchange. *Br. J. Haematol.* 164 (3), 342–351. doi: 10.1111/bjh.12629

Sammaritano, L. R., Bermas, B. L., Chakravarty, E. E., Chambers, C., Clowse, M. E. B., Lockshin, M. D., et al. (2020). 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol.* 72, 529–556. doi: 10.1002/art.41191

Sangle, S. R., Lutalo, P. M., Davies, R. J., Khamashta, M. A., and D'Cruz, D. P. (2013). B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. *J. Autoimmun.* 43, 55–59. doi: 10.1016/j.jaut.2013.03.001

Shieh, S., Fang, Y. V., Becker, J. L., Holm, A., Beutner, E. H., and Helm, T. N. (2004). Pemphigus, pregnancy, and plasmapheresis. *Cutis* 73, 327–329.

Slazinski, L., and Degefu, S. (1982). Herpes gestationis associated with choriocarcinoma. *Arch. Dermatol.* 118, 425–428. doi: 10.1001/archderm.1982.01650180059019

Soares, K. S., Lehmann, P. M., and Hofmann, S. C. (2018). Pemphigoid gestationis with lethal fetal malformation and postpartum persistence. *J. Dtsch. Dermatol. Ges.* 16, 775–777. doi: 10.1111/ddg.13540

Sun, D., Shehata, N., Ye, X. Y., Gregorovich, S., De France, B., Arnold, D. M., et al. (2016). Corticosteroids compared with intravenous immunoglobulin for the treatment of immune thrombocytopenia in pregnancy. *Blood* 128, 1329–1335. doi: 10.1182/blood-2016-04-710285

Tani, N., Kimura, Y., Koga, H., Kawakami, T., Ohata, C., Ishii, N., et al. (2015). Clinical and immunological profiles of 25 patients with pemphigoid gestationis. *Br. J. Dermatol.* 172, 120–129. doi: 10.1111/bjd.13374

Tavakolpour, S., Mirsafaei, H. S., and Delshad, S. (2017). Management of pemphigus disease in pregnancy. *Am. J. Reprod. Immunol.* 77. doi: 10.1111/aji.12601

Temprano, K. K., Bandlamudi, R., and Moore, T. L. (2005). Antirheumatic drugs in pregnancy and lactation. *Semin. Arthritis Rheumatol.* 35, 112–121. doi: 10.1016/j.semarthrit.2005.05.002

Terpstra, H., de Jong, M. C., and Klokke, A. H. (1979). In vivo bound pemphigus antibodies in a stillborn infant. Passive intrauterine transfer of pemphigus vulgaris? *Arch. Dermatol.* 115, 316–319.

Tourte, M., Brunet-Possenti, F., Mignot, S., Gavard, L., and Descamps, V. (2017). Pemphigoid gestationis: a successful preventive treatment by rituximab. *J. Eur. Acad. Dermatol. Venereol.* 31, e206–e207. doi: 10.1111/jdv.13962

Van de Wiel, A., Hart, H. C., Flinterman, J., Kerckhaert, J. A., Du Boeuff, J. A., and Imhof, J. W. (1980). Plasma exchange in herpes gestationis. *Br. Med. J.* 281, 1041–1042. doi: 10.1136/bmj.281.6247.1041-a

Vassallo, C., Grassi, S., Tagliabue, E., Piccolo, A., and Brazzelli, V. (2017). Pregnancy outcome after rituximab treatment before conception in patients affected by severe pemphigus vulgaris/superficialis. *J. Eur. Acad. Dermatol. Venereol.* 31, e331–e333. doi: 10.1111/jdv.14119

Veiga, V. F., Santos, F., Antunes, A., and Duarte, I. (2018). Pemphigoid gestationis. *BMJ Case Rep.*, bcr2018225242. doi: 10.1136/bcr-2018-225242

Zhao, C. Y., and Murrell, D. F. (2015). Autoimmune blistering diseases in females: a review. *Int. J. Womens Dermatol.* 1, 4–12. doi: 10.1016/j.ijwd.2015.01.002

Zhao, C. Y., Chiang, Y. Z., and Murrell, D. F. (2016). Neonatal Autoimmune Blistering Disease: A Systematic Review. *Pediatr. Dermatol.* 33, 367–374. doi: 10.1111/pde.12859

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

REVIEW
published: 11 November 2020
doi: 10.3389/fphar.2020.594042

Regulating Gut Microbiome: Therapeutic Strategy for Rheumatoid Arthritis During Pregnancy and Lactation

Yao Yao[1†], Xiaoyu Cai[2†], Weidong Fei[1], Fujia Ren[3], Fengmei Wang[1], Xiaofei Luan[1], Fengying Chen[1] and Caihong Zheng[1*]*

[1]Department of Pharmacy, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China, [2]Department of Pharmacy, Hangzhou First People's Hospital, Hangzhou, China, [3]Department of Pharmacy, Hangzhou Women's Hospital, Hangzhou, China

Rheumatoid arthritis (RA) is an autoimmune disease characterized by synovial inflammation and bone destruction. Microbial infection is considered to be the most important inducement of RA. The pregnancy planning of women in childbearing age is seriously affected by the disease activity of RA. Gut microbiome, related to immunity and inflammatory response of the host. At present, emerging evidence suggested there are significant differences in the diversity and abundance of gut microbiome during pregnancy and lactation, which may be associated with the fluctuation of RA disease activity. Based on these research foundations, we pioneer the idea of regulating gut microbiome for the treatment of RA during pregnancy and lactation. In this review, we mainly introduce the potential treatment strategies for controlling the disease activity of RA based on gut microbiome during pregnancy and lactation. Besides, we also briefly generalize the effects of conventional anti-rheumatic drugs on gut microbiome, the effects of metabolic changes during pregnancy on gut microbiome, alteration of gut microbiome during pregnancy and lactation, and the effects of anti-rheumatic drugs commonly used during pregnancy and lactation on gut microbiome. These will provide a clear knowledge framework for researchers in immune-related diseases during pregnancy. Regulating gut microbiome may be a potential and effective treatment to control the disease activity of RA during pregnancy and lactation.

Keywords: gut microbiome, rheumatoid arthritis, pregnancy, lactation, treatment

OPEN ACCESS

Edited by:
Maria Gerosa,
University of Milan, Italy

Reviewed by:
Caren Lee Hughes,
Mayo Clinic Florida, United States
Silvia M. Illamola,
University of Minnesota Twin Cities, United States

****Correspondence:***
Yao Yao
yaoyaofb@zju.edu.cn
Caihong Zheng
chzheng@zju.edu.cn

[†]These authors have contributed equally to this work and share first authorship.

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *12 August 2020*
Accepted: *05 October 2020*
Published: *11 November 2020*

Citation:
Yao Y, Cai X, Fei W, Ren F, Wang F, Luan X, Chen F and Zheng C (2020) Regulating Gut Microbiome: Therapeutic Strategy for Rheumatoid Arthritis During Pregnancy and Lactation. Front. Pharmacol. 11:594042. doi: 10.3389/fphar.2020.594042

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease characterized by synovitis and bone destruction (Cai et al., 2020). The pathogenesis of RA is not clear, but it is generally considered to be related to the interactions between genetic and environmental factors (Scherer et al., 2020). And at present, microbial infection is considered to be the most important inducement of RA (Li et al., 2013). RA is prevalent among women, the ratio of males to females is about 1:3, and it mostly occurs between

Abbreviations: CIA, collagen-induced arthritis; DMARDs, disease-modifying antirheumatic drugs; FMT, fecal microbiota transplantation; GDM, gestational diabetes mellitus; MTX, methotrexate; NLRs, Nod-like receptors; RA, rheumatoid arthritis; SCFAs, short-chain fatty acids; SFB, segmented filamentous bacteria; SGA, small for gestational age; SSZ, sulfasalazine; Th1/Th2/Th17, T helper cell 1/2/17; TLRs, Toll-like receptors; TTP, time to pregnancy.

20 and 55 years old (Croia et al., 2019). In the past decades, the exploration between RA and women indicated that the disease activity of RA fluctuate apparently during pregnancy and lactation. The disease activity of some patients with RA decreased during pregnancy, and some increased during lactation (de Man et al., 2008; Jethwa et al., 2019; Chen et al., 2020). These conditions seriously affect family planning and the health management of women in childbearing age.

Pregnancy is a complicated and delicate process, in which the maternal hormone levels, immunity and metabolism change conspicuously to ensure the normal growth and development of the fetus (Mu et al., 2019). As early as 1931, scholars began to study the relationship between RA disease activity and pregnancy or lactation. Here, a retrospective analysis based on objective markers of RA disease activity and related scores in 2019 showed that the disease activity of 60.3% of pregnant women with RA is improved during pregnancy and that of 46.7% is increased during lactation (Jethwa et al., 2019). What causes this phenomenon? Currently, it is generally believed that this is mainly associated with hormone levels of mother. Briefly, the level of estrogen with the anti-inflammatory effect increased significantly during pregnancy and decreased rapidly during lactation (Ince-Askan et al., 2017), which might be one of the important factors that cause the fluctuation in RA disease activity during pregnancy and lactation (de Jong and Dolhain, 2017). But this cannot explain the fact that many women are still having active disease activity during pregnancy and the proportion of improvement during pregnancy has gradually decreased for decades. The disease activity of RA during pregnancy and lactation severely affects the outcome of mother and fetus and postpartum health management (Bermas, 2017). However, apart from hormonal effects, the current understanding of the relationship between pregnancy or lactation and RA is very limited. Therefore, a clear demonstration of the impact of pregnancy and lactation on RA disease activity and its mechanisms is particularly important for managing the health of pregnant women with RA.

In recent years, the role of gut microbiome in the host health during pregnancy and lactation has received widespread attention. The maternal gut microbiome undergoes tremendous changes throughout pregnancy and lactation (Gomez-Arango et al., 2016b; Mutic et al., 2017; Stanislawski et al., 2017). This provides a novel idea for exploring the relationship between pregnancy or lactation and RA disease activity. During pregnancy and lactation, there are significant changes in the diversity, species richness, and composition of the maternal gut microbiome (Nuriel-Ohayon et al., 2016; Mu et al., 2019). The human gut microbiome is complex and composed of more than 500–1,500 different bacteria, archaea, fungi and viruses (de Brito Alves et al., 2019; DeMartino and Cockburn, 2020; Weersma et al., 2020). They are not only participating in the digestion and absorption of food but also play an important role in regulating immunity and metabolism of the host (Guerreiro et al., 2018; Peterson et al., 2020; Singh, 2020). Gut microbiome disorder leads to changes in microbial metabolites and increased permeability of the intestinal mucosa. These usually disrupt the balance between non-self antigen tolerance and immunity, which may promote antigen absorption and increase the persistence or worsening of immune-mediated diseases like RA (Morrison and Preston, 2016; Guerreiro et al., 2018; Picchianti-Diamanti et al., 2018).

More and more evidence showed that gut microbiome is involved in the formation of adaptive immunity and autoimmunity (Van de Wiele et al., 2016; Agorastos and Bozikas, 2019). The balance between helper T cell subsets and regulatory T cells is to be influenced by specific gut microbiome (Wu et al., 2010). For example, the colonization of *segmental filamentous bacteria* in mice can induce the production of Th17 cells. In contrast, *Clostridia* can induce the production of regulatory T cells, thereby suppressing the autoimmune response (Lee and Kim, 2017). Additionally, gut microbiome can directly or indirectly bind NOD-like receptors (Nod-like receptors) and/or Toll-like receptors (TLRs) to activate the immune system and produce metabolites of short-chain fatty acids (Short-chain fatty acids) (Hasegawa et al., 2006; Reichardt et al., 2014). Moreover, based on the study of gut microbiome at present, probiotics and specific gut microbiome metabolites are applicable in the treatment of various autoimmune diseases (Weis, 2018; Marietta et al., 2019).

In this review, we outline the role of gut microbiome in RA, specific changes in gut microbiome during pregnancy or lactation in recent years and the possibility of improving RA disease activity during pregnancy or lactation by regulating gut microbiome. Besides, we also briefly generalize the impacts of conventional anti-rheumatic drugs on gut microbiome, the effects of metabolic changes during pregnancy on gut microbiome, the outcome of mothers and fetuses in pregnant women with RA (Preterm delivery, Cesarean section, small for gestational age), and the anti-rheumatic drugs commonly used during pregnancy and lactation. This review will provide a clear knowledge framework for researchers in the field of pregnancy-related immune diseases. Regulating gut microbiome might be a potential and effective treatment to control the disease activity of RA during pregnancy and lactation.

THE ROLE OF GUT MICROBIOME IN RHEUMATOID ARTHRITIS

Gut Microbiome in the Etiology of Rheumatoid Arthritis

RA is an inflammatory autoimmune disease characterized by synovial inflammation and bone destruction (Yao et al., 2018; Yao et al., 2019). The pathogenesis of RA is complicated, including the interaction between innate immune response and acquired immune response, which involves the formation of self-reactive T cells, antigen presentation and the formation of autoantibodies. These autoantibodies may come from various parts of the body, such as the gastrointestinal tract, and eventually enter the blood circulation, causing systemic joint inflammation (Malmstrom et al., 2017; Favalli et al., 2019).

The studies showed that the development of RA is based on heredity and epigenetics, but environmental factors also play an important role, such as cigarette smoke and dust contact, especially the microbiome representing the "internal" environment (**Figure 1**) (Amariuta et al., 2020; Scherer et al., 2020). And the susceptibility of

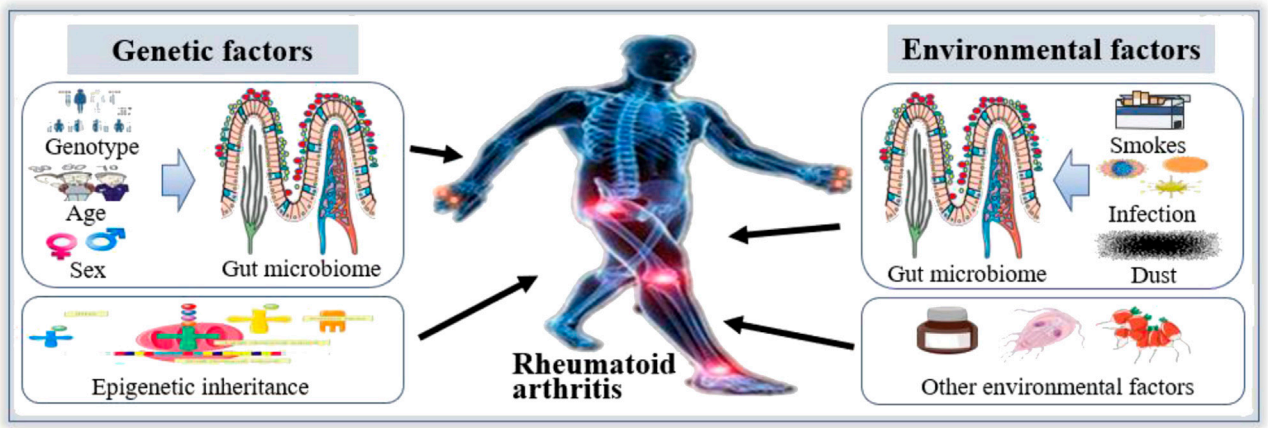


FIGURE 1 | Gut microbiome in the etiology of Rheumatoid arthritis (RA). The etiology of RA is mainly related to environmental factors and genetic factors. Among the environmental factors, smoking, infection and dust can affect the structure of gut microbiome to participate in the occurrence and development of RA. Among genetic factors, the composition of gut microbiome is associated with genotype and sex, which is linked to the occurrence and development of RA. Therefore, gut microbiome play an important role in the etiology of RA.

RA is related to environmental factors, such as smoking and infection, which may be mediated by gut microbiome (Klareskog et al., 2006; Luckey et al., 2013). In particular, genotype and sex are strong determinants of gut microbiome, although gut microbiome changes dynamically with age (Gomez et al., 2012; Morgan et al., 2012). In humans, age-related alterations of gut microbial composition are associated with enrichment of pathobionts (Yatsunenko et al., 2012; Rampelli et al., 2013). These changes may cause an increase or loss of intestinal metabolic function, leading to disorders of gut microbiome. Additionally, smoking has been shown to affect the diversity of gut microbiome and quitting smoking will increase the diversity of gut microbiome (Biedermann et al., 2013; Savin et al., 2018). These findings indicate that the decrease in the diversity of gut microbiome is one of the reasons for the development of RA.

With the increased understanding of gut microbiome, there has been a wide area of related researches, especially in autoimmune diseases. The evidence supporting the association of gut microbiome with RA is as follows: 1) Compared with the control group, the composition of gut microbiome changed in early RA patients, the abundance of certain bacteria in the genus Bifidobacterium and *Bacteroides* decreased, and genus Prevotella increased significantly (Vaahtovuo et al., 2008; Bernard, 2014; Jeong et al., 2019). 2) In the germ-free model, parenteral injection of cell wall fragments of exogenous intestinal bacteria can induce arthritis (Scher et al., 2013; Bernard, 2014). 3) Partial gut microbiome of clinical RA patients restored to normality after antirheumatic treatment (Zhang et al., 2015; Bodkhe et al., 2019). 4) Existing reports have shown that diet could affect the activity of inflammation, and high-fat diet has a negative effect on intestinal permeability (Skoldstam et al., 2003; Rohr et al., 2020). 5) Many drugs for the treatment of RA have antibacterial properties, such as minocycline, chloroquine, roxithromycin and sulfadiazine (Ogrendik, 2009; Ogrendik and Karagoz, 2011). 6) The alpha diversity index of gut microbiome in the feces of RA patients is significantly lower than that of healthy people. The bacterial genera *Bacteroides* and Escherichia-Shigella were more abundant in RA patients. In contrast, *Lactobacillus*, *Odoribacter*, *Enterobacter*, and *Alloprevotella* were less abundant in RA patients than that in healthy people (Drago, 2019; Sun et al., 2019). Based on the above facts, we conclude that gut microbiome may be closely related to RA, and the imbalance of gut microbiome may be one of the causes of RA.

The Mechanism of Gut Microbiome in Rheumatoid Arthritis

The studies of gut microbiome in animal models, the effects of diet and probiotics on the extent of inflammatory activity support the potential role of gut microbiome in the pathogenesis of RA (Badsha, 2018; Jubair et al., 2018). Researches in RA patients or animal models indicated that the abundance of many genera of gut microbiome increased or decreased significantly compared with the control group (healthy people or animal). The influence mechanism of gut microbiome on the pathophysiology of RA may be multifactorial, and it mainly includes the following aspects: the ability to produce citrullinization of peptides by enzymatic action, activation of antigen-presenting cells through an effect on TLRs or NLRs, antigenic mimicry, control of host immune system (triggering T cell differentiation), alterations in permeability of intestinal mucosal, and increase of T helper type 17-mediated mucosal inflammation [**Table 1** (Round et al., 2011; Marietta et al., 2016; Teng et al., 2016; Pahari et al., 2017; Guo et al., 2019; Li et al., 2020; McHugh, 2020; Tajik et al., 2020)].

The evidence related to gut microbiome participating in the pathogenesis of RA all came from animal experiments based on the current research. In humans, it is only proven that there is a difference in gut microbiome between RA patients and healthy people, which cannot clarify the causal relationship between RA and gut microbiome. To predict the role of gut microbiome in the pathogenesis of RA, an improved understanding related to gut

TABLE 1 | The mechanism of gut microbiome in RA (animal experiment).

Experimental model	Bacteria involved	Analytical method	Mechanism	References
K/BxN mice, induced arthritis	*Segmented filamentous bacteria (SFB)*	*SFB*-specific 16S rRNA quantitative PCR	SFB enhance autoimmune arthritis, reflected by elevated auto-ab, GC, and tfh cell responses. SFB induce Peyer's patch T follicular helper cell differentiation by limiting the access of IL-2 to Peyer's patch $CD4^+$ T cells	(Teng et al., 2016)
Wistar female rat, collagen-induced arthritis	Rarefaction and α diversity of gut microbiome	16S rRNA gene sequencing	Saponins alleviation collagen-induced arthritis in rats by regulating metabolites of gut microbiomes (short-chain fatty acids, C_2–C_6)	(Guo et al., 2019)
Experimental arthritis	Particular bacteria genera	Not applicable	Microbiota-derived metabolites help regulatory B cells suppress arthritis	(McHugh, 2020)
Female RA patients and collagen-induced arthritis mice	Gut microbiota composition	16S rRNA microbiome analysis	Breach in intestinal permeability is mediated by the microbiota. Reducing intestinal barrier permeability attenuates rheumatoid arthritis	(Tajik et al., 2020)
SD rat, collagen-induced arthritis	*Bacteroides* and *Bacillus,* α diversity of gut microbiome	16S rRNA gene sequencing	Gut microbiota regulated the aryl hydrocarbon receptor pathway through indole metabolism. Regulating host immunity	(Li et al., 2020)
Expert protein analysis system	The microbial peptides	Immunoinformatics tools	Molecular mimicry, antigenic mimicry	(Pahari et al., 2017)
Transgenic mice, collagen-induced arthritis	*Prevotella histicola*	Isolation of *Prevotella species*, and administered enterally	Enteral exposure to *Prevotella histicola* suppresses arthritis via mucosal regulation	(Marietta et al., 2016)
Different TLR-deficient mice	*Bacteroides fragilis*	*Bacteroides fragilis* colonization	Toll-like receptor 2 on $CD4^+$ T cells is required for *Bacteroides fragilis* colonization of a unique mucosal niche in mice during homeostasis	(Round et al., 2011)

RA, Rheumatoid arthritis. The possible mechanisms of gut microbiome in RA (only animal experiment) are showed in this table.

TABLE 2 | The effect of some DMARDs on gut microbiome.

DMARDs	Pharmacological mechanism	Species studied	Effects on gut microbiome	References
Sulfasalazine	Interferes in the conversion of arachidonic acid to prostaglandins, affects leukocyte function and production of cytokines	Human	Significant increase in *bacillus* and decrease in total erobic bacteria, *Escherichia coli* and *Bacteroides*	(Kanerud et al., 1994)
		Human	Reduction in the numbers of total nonsporing anaerobes, *Enterobacteria* and opalescentnegative clostridia	(West et al., 1974)
Methotrexate	Interferes with the synthesis of pyrimidine and purines, leads to the inhibition of lymphocyte proliferation	Balb/c mice	Decrease in *Bacteroides fragilis* post-treatment	(Zhou et al., 2018)
		Human	Reduced abundance of Enterobacteriaceae	(Picchianti-Diamanti et al., 2018)
		Human	Partially restored the gut microbiota in patients	(Zhang et al., 2015; Chen et al., 2016)
Hydroxychloroquine	Interferes with antigen processing in macrophages and its presentation to MHC class II proteins	Human	Increase in microbial species richness and diversity	(Chen et al., 2016)
		Human	Hydroxychloroquine plus doxycycline treatment led to the reduction in abundance of phylum *Bacteroidetes* and *Firmicutes*	(Angelakis et al., 2014)

DMARD, disease-modifying antirheumatic drug. The drugs used to treat RA are mainly DMARDs, which plays an important role in controlling the symptoms and progression of the disease. In DMARDs, Sulfasalazine, Methotrexate and Hydroxychloroquine have an effect on gut microbiome.

microbiome of the ecology and interactions with other microorganisms and hosts is still needed. Furthermore, the interaction between gut microbiome and the immune system might be the most likely influencing factor for gut microbiome to participate in the pathogenesis of RA, especially the influence of gut microbiome on Th17 cells. And the in-depth study of animal experiments will lay a solid foundation for clinical research.

Rheumatoid Arthritis Treatment Based on Gut Microbiome

The pathogenesis of RA is considered to be the result of the interaction between genetics and the environment. The drugs used to treat RA are mainly disease-modifying antirheumatic drugs (DMARDs), which play an important role in controlling the symptoms and progression of the disease (Burmester and Pope, 2017). Recently, more and more evidence showed that gut microbiome regulates the host immune system directly or indirectly, for example, some gut microbiome in RA patients returned to normal after treatment with DMARDs (Bodkhe et al., 2019). Microbiome refers to a collection of genomes within an ecological community of microorganisms (Boon et al., 2014). It is difficult to clarify the role and mechanism of gut microbiome in human diseases due to only about 1% of microbes are culturable (Prakash et al., 2013). Fortunately, the development of DNA sequencing technology has made it possible to study unculturable microbes (The Human Microbiome Project Consortium, 2012; Ranjan et al., 2016). Gut microbiome has a strong metabolic potential and an important influence on the stability and activity of drugs that enter the intestine (Vande Voorde et al., 2014; Lehouritis et al., 2015). For example, the action of sulfasalazine (SSZ, a drug used to treat RA) must depend on anaerobic bacteria in the colon (Sousa et al., 2014). Moreover, drug treatment also has a significant effect on the composition of gut microbiome in the host (Sousa et al., 2008; Maier et al., 2018). Therefore, alterations of gut microbiome caused by drug affect the therapeutic effect and the host's immune response [**Table 2** (West et al., 1974; Kanerud et al., 1994; Angelakis et al., 2014; Zhang et al., 2015; Chen et al., 2016; Picchianti-Diamanti et al., 2018; Zhou et al., 2018)].

The drugs currently used to treat RA mainly include traditional DMARDs, biologic DMARDs, biologics, and alternative medicines such as herbs and probiotics (Demoruelle and Deane, 2012). Traditional DMARDs such as leflunomide, methotrexate (MTX), SSZ and hydroxychloroquine are essential in the treatment of RA (Scher et al., 2013). Compared with the control group, the gut microbiome diversity of RA patients increased and the disease activity of RA decreased after receiving these drugs (Zhang et al., 2015; Chen et al., 2016). **Table 2** summarizes the effects of some DMARDs on gut microbiome (West et al., 1974; Kanerud et al., 1994; Angelakis et al., 2014; Zhang et al., 2015; Chen et al., 2016; Picchianti-Diamanti et al., 2018; Zhou et al., 2018). In general, biologic DMARDs (bDMARDs) will be considered when RA patients are not effective in the treatment of traditional DMARDs. As with traditional DMARDs, treatment with bDMARDs also causes changes in the abundance of gut microbiome (Picchianti-

Diamanti et al., 2018). For example, with the treatment of etanercept (belongs to bDMARDs), the abundance of *Cyanobacteria* in the intestine increased significantly compared with untreated patients (Bodkhe et al., 2019). Chinese herbal medicine has been used to treat various incurable diseases since ancient times (Rigau-Perez, 2016). In recent years, a relationship between the therapeutic effect of Chinese herbal medicine and gut microbiome has been proved by researchers. Xiao M et al. found that the diversity of gut microbiome increased in collagen-induced arthritis mice treated with *Paederia scandens* (Chinese herbal medicine) (Xiao et al., 2018). In addition, the therapeutic effect of another Chinese herbal medicine, *Tripterygium wilfordii* (Chinese herbal medicine), used to treat RA has also been shown to be related to gut microbiome (Miao et al., 2015). After receiving the treatment of *Tripterygium wilfordii*, the abundance of *Prevotella intermedia* in the intestine of RA patients was increased (Zhang et al., 2015). What's more, the direct application of probiotics proves the importance of regulating gut microbiome to RA (Pineda Mde et al., 2011; Vaghef-Mehrabany et al., 2014). Therefore, the treatment of RA based on gut microbiome may be a potential and effective strategy.

GUT MICROBIOME IN PREGNANCY AND LACTATION

Alterations of Gut Microbiome During Pregnancy

Pregnancy is a complex and delicate process with remarkable changes in the hormone level, immunity and metabolism of the mother to ensure the successful growth and development of the fetus (Pazos et al., 2012; Fejzo et al., 2019). The immune system and some complications during pregnancy are related to gut microbiome (Nyangahu et al., 2018; de Brito Alves et al., 2019). Several studies have proved that microbial infections such as bacteria, fungi or viruses during pregnancy are important risk factors for adverse pregnancy outcomes, including eclampsia, premature rupture of membranes, recurrent miscarriage, intrauterine growth retardation and premature delivery (Lamont, 2015; Young et al., 2015). Notably, there is a conspicuous change in the diversity of gut microbiome during the process of pregnancy (Chen et al., 2017). The whole microbial community undergoes an amazing rearrangement related to the host's physiology and immunity (Koren et al., 2012; Paysour et al., 2019). Recently, some scholars suggested that gut microbiome remodeling during pregnancy is a positive reaction of the mother and necessary for a successful pregnancy, which may contribute to the state of the immunity and metabolism (Konstantinov et al., 2013). However, more researchers believe that changes in gut microbiome during pregnancy are harmful to pregnant women and will cause related complications (Morffy Smith et al., 2019).

The physiological changes of pregnant women are accompanied by the alteration of microbes, especially gut microbiome (Koren et al., 2012; Edwards et al., 2017). The gut microbiome of first trimester is similar in many aspects to that of healthy nonpregnant male and female controls. However, by the third trimester, the structure and composition of the community resemble a disease-associated dysbiosis that differs among women (Koren et al., 2012). Generally, pregnancy is characterized by increased bacterial load and profound changes in the composition of intestinal microorganisms (Nuriel-Ohayon et al., 2016; Smid et al., 2018). During pregnancy, the changes of gut microbiome mainly include the decrease of individual richness (α diversity), the change of specific species richness and the increase of between-subject diversity (β diversity) (Koren et al., 2012; Chen et al., 2017). **Table 3** summarizes alterations of gut microbiome during pregnancy (Koren et al., 2012; Gohir et al., 2015; Smid et al., 2018; Chen Y. et al., 2019; Ji et al., 2019; Liu et al., 2019).

Factors Affecting Gut Microbiome During Pregnancy

The initial changes in the mother during pregnancy are hormone levels. Progesterone and estrogen levels rise sharply, which cause many physiological effects (Di Renzo et al., 2016; Hudon Thibeault et al., 2019). On the one hand, these hormone levels are likely to affect the structure of gut microbiome because it has been proven that the composition of microorganisms is involved in responding and regulating host hormone levels, and host hormone levels affect bacterial growth (Gomez-Arango et al., 2016a). On the other hand, microorganisms can also secrete or produce hormones. Therefore, the interaction between hormones and microorganisms is bidirectional, and the two interact with each other (Neuman et al., 2015). However, there is a lack of direct evidence for the effect of gut microbiome on these hormones and the effect of estrogen or progesterone on gut microbiome. Further research is necessary. Besides, the immune system of mothers changes during pregnancy to support the successful growth of the fetus. Many studies have proven that gut microbiome participates in the regulation of the immune system, and the possible mechanism is antigen simulation or change in intestinal permeability (Rooks and Garrett, 2016; Neuman and Koren, 2017).

Apart from hormones, the relationship between metabolic changes during pregnancy and gut microbiome has received widespread attention at present. Metabolic changes during pregnancy are very similar to those in metabolic syndrome, including changes in metabolic hormone levels, weight gain, glucose intolerance, elevated fasting blood glucose levels, low-grade inflammation, and insulin resistance (Meo and Hassain, 2016; Nuriel-Ohayon et al., 2016; Zeng et al., 2017). These changes are closely connected with the composition of gut microbiome. **Table 4** summarizes the effects of different metabolic changes during pregnancy on gut microbiome (Collado et al., 2008; Santacruz et al., 2010; Gohir et al., 2015; Kuang et al., 2017; Crusell et al., 2018).

Alterations of Gut Microbiome During Lactation

Lactation refers to the period from a mother secretes milk from her mammary glands to the stop of breastfeeding, which generally

TABLE 3 | Alteration of gut microbiome during pregnancy.

Bacterial Taxa (↓ low, ↑ enriched)	Research object	Relevant conclusions	Analytical method	References
Proteobacteria ↑, *Actinobacteria* ↑, *Faecalibacterium* ↓	Normal women third trimester VS. non-pregnant women	Gut microbiomes are profoundly altered during pregnancy	16S rRNA gene sequencing	(Koren et al., 2012)
Clostridiales ↑, *Desulfovibrio* ↑, *Mogibacteriaceae* ↑, *Prevotella* ↑	Normal pregnant sows VS. non-pregnant sows	Stages of pregnancy influence the gut microbiota diversity and function in sows	16S rRNA gene sequencing	(Ji et al., 2019; Liu et al., 2019)
Firmicutes ↓, *Bacteroidetes* ↓, *Ruminococcaceae* ↓, *Akkermansia* ↑	Normal pregnant women, from 32 weeks of gestation to antepartum VS. non-pregnant women	The gut microbiota varied during the third trimester	16S rRNA gene sequencing	(Chen et al., 2019b)
Proteobacteria (ET2) ↑	Healthy women, early second trimester (ET2) VS. late second trimester	Maternal microbiome biodiversity changes as pregnancy progresses	16S rRNA gene sequencing	(Smid et al., 2018)
Akkermansia ↑, *Clostridium* ↑, *Bacteroides* ↑, *Bifidobacterium* ↑	Normal pregnant mice VS. non-pregnant mice	Pregnancy-induced changes in the female gut microbiota occur immediately at the onset of pregnancy	16S rRNA gene sequencing	(Gohir et al., 2015)

The structure of gut microbiome is connected with pregnancy. The changes of specific flora, the analytical method used and the research object are summarized in this table.

lasts for 10–12 months. The level of prolactin in postpartum mothers increased significantly, while the level of progesterone decreased rapidly (Vieira Borba and Shoenfeld, 2019). As mentioned above, changes in hormones affect the structure of gut microbiome. At present, the study of gut microbiome in lactation is less than that in pregnancy. Unlike the fluctuations observed during gestation, the bacterial composition appeared to be relatively stable over different stages of lactation (Liu et al., 2019). Liu et al. found that Christensenellaceae, Lachnospiraceae, and *Escherichia coli* are enriched during lactation in sows (Liu et al., 2019). Besides, another analysis of gut microbiome of the sow from pregnancy to weaning showed that the abundance of *Tenericutes* during lactation is significantly increased while *Bacteroidetes* and *Fibrobacteres* are decreased (Ji et al., 2019). These studies indicate that the gut microbiome during lactation is also in a state of disorder and continues the characteristics of pregnancy. The diversity of gut microbiome during lactation is similar to that in late pregnancy, and there was no significant change over time (Jost et al., 2014). However, we need more evidence to demonstrate the characteristic of gut microbiome in lactation. The difference between gut microbiome in lactation and normal women needs to be clarified to explore the specific genus of gut microbiome during lactation. This may help us to further study the role and mechanism of gut microbiome in disease states and to manage the health of lactating women.

In addition to lactation, there are also significant differences in the composition of gut microbiome in postpartum women. Operational taxonomic units richness and Shannon index decreased from late pregnancy to postpartum regardless of metabolic status (Crusell et al., 2018; Hasan et al., 2018). However, it lack of evidence to demonstrate the difference between breastfeeding and non-breastfeeding women, and further researches are needed.

THE TREATMENT OF RHEUMATOID ARTHRITIS DURING PREGNANCY AND LACTATION BASED ON GUT MICROBIOME

Fluctuation of Disease Activity During Pregnancy and Lactation, and Feasibility of the Treatment Based on Gut Microbiome

RA is common among women, and the ratio of men to women is close to 1:3. In women with RA, it seems to be more difficult to conceive, and the disease activity affects the mother and fetal outcome (Wallenius et al., 2011; Wallenius et al., 2012; Yao et al., 2020). For example, RA patients have a longer time to pregnancy (TTP). **Table 5** summarizes some studies on pregnancy outcomes of RA patients (Nelson et al., 1992; Skomsvoll et al., 1999; Reed et al., 2006; de Man et al., 2009; Lin et al., 2010; Norgaard et al., 2010; Brouwer et al., 2015b). The disease activity of some patients usually improves during pregnancy. However, a large number of RA patients (>50%) still suffer from active diseases during pregnancy. Thus, clinical treatment is necessary, especially considering the negative correlation between active diseases and pregnancy outcomes (de Jong and Dolhain, 2017). At

TABLE 4 | Effects of different metabolic changes during pregnancy on gut microbiome.

Bacterial Taxa (↓ low, ↑ enriched)	Analytical method	Research object information	Relevant conclusions	References
Actinobacteria phylum ↑, *Collinsella* genus ↑, *Rothia* genus ↑, *Desulfovibrio* genus ↑	16S rRNA gene amplicon sequencing	Third trimester, gestational diabetes mellitus (GDM)	GDM diagnosed in the third trimester of pregnancy is associated with a disrupted gut microbiota composition compared with normoglycaemic pregnant women	(Crusell et al., 2018)
Bacteroides ↑, *Staphylococcus* ↑	FISH combined with flow cytometry and qPCR	Overweight pregnant women	Gut microbiota composition and weight are linked, and mothe's weight gain is affected by microbiota	(Collado et al., 2008)
Allobaculum ↑, *Sarcina* ↑, *Biophila* ↑, *Coprobacillus* ↑, *Staphylococcus* ↑, *Akkermansia* ↑, *Bifidobacterium* ↑	16S rRNA gene sequencing	Pregnant 5C7BL/6 mice with high-fat diet	Shifts in the maternal gut microbiome have been implicated in metabolic adaptations to pregnancy	(Gohir et al., 2015)
Parabacteroides distasonis ↑, *Klebsiella varicola* ↑, *Methanobrevibacter smithii* ↓, *Alistipes spp.* ↓, *Bifidobacterium spp.* ↓, *Eubacterium spp.* ↓	Whole-metagenome shotgun sequencing	Pregnant women with gestational diabetes mellitus	The human gut microbiome can modulate metabolic health and affect insulin resistance, and it may play an important role in the etiology of gestational diabetes mellitus	(Kuang et al., 2017)
Bifidobacterium ↓, *Bacteroides* ↓, *Staphylococcus* ↑, Enterobacteriaceae ↑, *Escherichia coli* ↑	Quantitative real-time PCR	24 weeks of pregnancy, overweight pregnant women	Gut microbiomes composition is related to body weight, weight gain and metabolic biomarkers during pregnancy	(Santacruz et al., 2010)

Compared with normal healthy women, the abundance and diversity of gut microbiome during pregnancy are significantly different. This may be related to the mother's hormone levels and metabolism. The effects of metabolism on gut microbiome during pregnancy are summarized in this table.

present, during pregnancy and lactation, antirheumatic drugs are mainly used to control disease activities. The main side effect of the approved antirheumatic drugs could increase TTP, including nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone (in a dose >7.5 mg daily) (Brouwer et al., 2015a). In addition, the use of MTX may damage fertility (Provost et al., 2014). Therefore, a treat-to-target strategy aiming for low disease activity is recommended for RA patients with the plan of conceive.

RA improves during pregnancy and relapses during lactation, but the improvement effect is not as previously thought (Gerosa et al., 2016). This results in a substantial number of RA patients with moderate to high disease activity during pregnancy (Ince-Askan and Dolhain, 2015). Therefore, how to take a scientific and reasonable plan to improve the maternal and infant outcomes and improve or control the condition of these patients has become the focus of clinical research in the field of rheumatism. The causes of the disease activity in pregnancy and lactation are still unclear at present. Through the study of pregnancy and RA and reviewing the relevant reports at home and abroad in recent years, we summarized the possible mechanisms as follows: 1) After pregnancy, the increase in progesterone and estrogen causes the level of glucocorticoid to rise, and estrogen itself also has anti-inflammatory effects. 2) The conversion of hormone secretion after pregnancy, the balance of Thl/Th2 type immune response and the activity of T cells can be indirectly regulated and suppressed by higher levels of estrogen. 3) Changes in regulatory T cell subsets can reduce the immune response to inflammation, which not only makes the mother immune tolerance to the fetus but also reduces the immune response to RA. 4) The conversion of postpartum hormone secretion makes the level of hormones with anti-inflammatory effect drop rapidly so that the pro-inflammatory effect of Th1-related cytokines is dominant. 5) Prolactin influences the negative selection of autoreactive B cells, promoting their proliferation, survival, and antibody production.

However, mechanisms of the fluctuation of RA disease activity during pregnancy and lactation are mainly based on the level of hormones. These cannot explain the decrease in improvement rate of RA during pregnancy in recent years. The improvement of RA during pregnancy can be attributed to not just a single mechanism but most likely several different pathogenic mechanisms (Ince-Askan and Dolhain, 2015; Murakawa, 2016). Controlling RA disease activity during pregnancy and lactation is challenging, especially because several antirheumatic drugs are contraindicated in pregnancy (Forger and Villiger, 2016; Ngian et al., 2016). Extensive studies on gut microbiome in RA and pregnancy revealed that gut microbiome might play an important role in pregnancy with RA. Changes in the diversity of gut microbiome during pregnancy and lactation may be one of the key factors in the fluctuation of RA disease activity. Moreover, compared with anti-rheumatic drugs, regulating the gut microbiome to control the disease activity of RA may be safer for pregnant women and fetuses. Based on the recent studies of gut microbiome between RA and pregnancy or lactation, we propose a new treatment strategy: regulating gut microbiome. Here, we summarize several methods for the treatment of RA during pregnancy and lactation based on gut microbiome.

TABLE 5 | Some studies on pregnancy outcomes of RA patients.

Number of patients	Increased risk	Study type	References
4,716 female patients with inflammatory arthritis (RA, juvenile RA, ankylosing spondylitis) vs. 1,645,029 unaffected female controls	Preterm delivery (7.1 vs. 5.6%), SGA infants (9.9 vs. 8.7%)	Retrospective (birth registry)	(Skomsvoll et al., 1999)
243 female RA patients vs. 2,559 unaffected female controls	Preterm delivery (13.6 vs. 7.2%), cesarean section (34 vs. 19.5%)	Retrospective (birth registry)	(Reed et al., 2006)
1,199 female RA patients vs. 870,380 unaffected female controls	Preterm delivery (9.2 vs. 6.2%), SGA infants (5.9 vs. 3.8%)	Retrospective (birth registry)	(Norgaard et al., 2010)
144 female RA patients vs. 605 unaffected female controls	No increased risk: spontaneous abortions, stillbirths	Case–control	(Nelson et al., 1992)
1,912 female RA patients vs. 9,560 matched controls	SGA infants (17.3 vs. 14.9%), cesarean section (42 vs. 37.7%), preeclampsia (2.7 vs. 1.2%)	Retrospective (birth registry)	(Lin et al., 2010)
152 female RA patients vs. 175,498 unaffected female controls	Instrumental vaginal delivery (17 vs. 10%), cesarean sections group with DAS28-CRP ≥3.2 (22 vs. 10% in group with DAS28–CRP <3.2%), SGA infants 3.3%	Prospective	(de Man et al., 2009)
162 female RA patients vs. general Dutch population	No increased risk: miscarriage	Prospective	(Brouwer et al., 2015b)

SGA, small for gestational age; RA, Rheumatoid arthritis. The adverse pregnancy outcomes of RA patients are summarized.

Therapeutic Method Based on Gut Microbiome

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) therapy refers to the transfer of fecal microbial extracts from healthy donors to diseased recipients through colonoscopy, oral, nasogastric tube, nasal duodenum, or enema, to reconstruct the complete intestinal microbial community and reverse the imbalance of microecology (Vindigni and Surawicz, 2017; Wang et al., 2019). The research on FMT could be traced back to 1958. Four patients with pseudomembranous colitis survived through FMT (Eiseman et al., 1958). At present, FMT is mainly used to combat *Clostridium difficile* infectious colitis, and the cure rate can reach 90% (Vindigni and Surawicz, 2017). Additionally, FMT is also used in other diseases, such as Parkinson's disease, obesity and metabolic syndrome, cancer, and multiple sclerosis (Choi and Cho, 2016; Chen D. et al., 2019; Zhou et al., 2019). FMT has not been used in patients with RA. However, when discussing the potential application of this method in inflammatory arthritis, some scholars suggested that the research results of FMT in inflammatory bowel disease are related to inflammatory arthritis. Especially compared with ulcerative colitis, there is a stronger association between spinal arthritis and Crohn's disease (Abdollahi-Roodsaz et al., 2016). Therefore, FMT may be a therapeutic method for improving RA disease activity during pregnancy after the mechanism of gut microbiome in pregnancy with RA has been elucidated.

Prebiotics or Probiotics Supplementation

Prebiotics is an indigestible food ingredient that selectively stimulates the growth and activity of probiotics in the intestine, thereby improving host health (Naseer et al., 2020; Ricke et al., 2020). It is currently defined as "a substrate that is selectively utilized by host microorganisms endowed with health benefits," and its "selectivity" mainly refers to *Lactobacillus* and *Bifidobacterium* (da Silva et al., 2020). Oral prebiotics supplements, especially those added with plant polysaccharides, are effective to improve gut microbiome (Roberfroid et al., 2010). Probiotics are beneficial to human health, such as *Bifidobacterium*, *Lactobacillus* and *Yeast* (Morovic and Budinoff, 2020). Probiotics/prebiotics is widely used in the medical field to prevent or treat some diseases, and their therapeutic effect on RA has been confirmed in animals and humans (Mohammed et al., 2017). Probiotics/prebiotics intervention may be a safe and effective method to regulate gut microbiome.

Reasonable Use of Antibiotics

The treatment of gut microbiome also includes the use and management of antibiotics (Iizumi et al., 2017). Different kinds of antibiotics have different effects on gut microbiome (Lange et al., 2016). A study showed that the delayed onset of RA flares after the use of specific antibiotics might be mediated through the gut microbiome (Nagra et al., 2019). However, the use of antibiotics during pregnancy could affect the health of infant and the exposure of the breastfed infant to antibiotics is

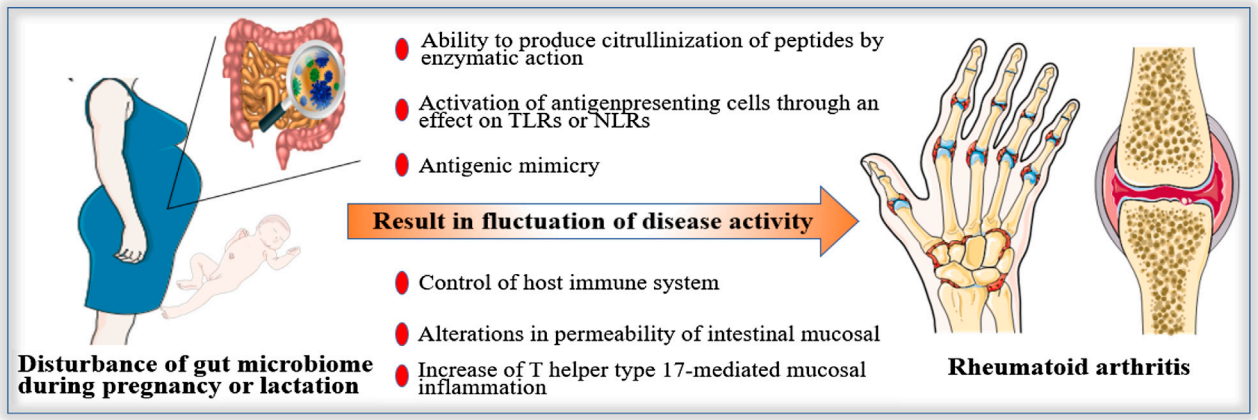


FIGURE 2 | Possible mechanisms of gut microbiome in Rheumatoid arthritis (RA) during pregnancy and lactation. The fluctuation of disease activity of RA during pregnancy and lactation may be affected by gut microbiome. The possible mechanisms are as follows: 1) The ability to produce citrullinization of peptides by enzymatic action. 2) Activation of antigenpresenting cells through an effect on Toll-like receptors or Nod-like receptors. 3) Antigenic mimicry 4) Control of host immune system (triggering T cell differentiation). 5) Alterations in permeability of intestinal mucosal. 6) Increase of T helper type 17-mediated mucosal inflammation.

related to bacterial resistance and the development of gut microbiome (van Wattum et al., 2019; Zimmermann and Curtis, 2020). Therefore, the use of antibiotics to regulate gut microbiome during pregnancy should be carefully considered. And reasonable use of antibiotics can effectively control the disease activity of RA during pregnancy or lactation.

Gut Pharmacomicrobiomics

The ability of gut microbiome to metabolize drugs is comparable to that of the liver (Enright et al., 2016). Gut pharmacomicrobiomics reflects the influence of changes in gut microbiome on drug pharmacokinetics and pharmacodynamics (Saad et al., 2012; Doestzada et al., 2018). Most drugs have little contact with gut microbiome because they are rapidly and completely absorbed by the upper gastrointestinal tract (Kim, 2015). However, some drugs are converted into active, inactive or toxic metabolites by gut microbiome located in the ileum and colon (Wilson and Nicholson, 2017). For example, the antirheumatic drug sulfasalazine is broken down into sulfapyridine and 5-aminosalicylic acid by the bacterial azoreductase in the colon, which is not metabolized when antibiotics are given (Peppercorn and Goldman, 1972). Pharmacomicrobiomics based on gut microbiome may be a potential treatment for RA during pregnancy or lactation. Current research needs to further clarify the mechanism of interaction between gut microbiome and drugs. The intervention of enzymes produced by specific bacteria may be of great significance for the treatment of RA during pregnancy or lactation.

Diet Regulation

Gut microbiome could be involved in energy balance by affecting the efficiency of energy harvesting from the diet and the expression of host genes related to the regulation of energy storage and expenditure (Guo et al., 2018). It is well known that diet is closely related to obesity and hyperlipidemia. Obesity and hyperlipidemia have a great influence on gut microbiome during pregnancy. The abundance of the phylum Firmicutes was lower and *Bacteroidetes* was higher in strict vegetarians, with the genus Prevotella being increased among other changes (Franco-de-Moraes et al., 2017). A randomized controlled trial showed that differences exited in the relative abundance of several genera in pregnancy women on a vegetarian diet, specifically a reduction in *Collinsella*, *Holdemania*, and increases in the relative abundances of *Roseburia* and Lachnospiraceae (Barrett et al., 2018). Therefore, diet control may be an effective treatment method for RA during pregnancy or lactation.

DISCUSSION

Presently, there is limited knowledge about the fluctuation of RA activity during pregnancy or lactation in addition to hormonal effects. We speculate that the changes of gut microbiome during pregnancy are harmful to the disease activity of RA based on current studies. The improvement of the disease activity of RA during pregnancy may be the result of neutralization between the harmful effects of gut microbiome and the beneficial effects of estrogen and progesterone. From late pregnancy to lactation, the levels of estrogen and progesterone decreased rapidly, and the leading role of gut microbiome appeared, showing the recurrence of RA at this time. Therefore, regulation of gut microbiome may be a potential strategy for the treatment of RA during pregnancy and lactation. Combined with domestic and foreign literature reports, the treatment of RA based on gut microbiome mainly includes fecal microbiota transplantation, prebiotics or probiotics supplementation, reasonable use of antibiotics, gut pharmacomicrobiomics and diet regulation.

However, current knowledge in this field is limited. Most studies related to gut microbiome during pregnancy or lactation

are animal experiments. Therefore, there is a long journey before conclusion, the first step is to clarify the difference of gut microbiome between pregnant women with RA and healthy pregnant women. Then the specific bacteria associated with pregnancy with RA and its mechanism should be demonstrated. Finally, the method based on regulating gut microbiome to improve the disease activity of RA during pregnancy or lactation should be explored. The mechanisms of gut microbiome in RA during pregnancy and lactation may be (**Figure 2**): 1) The ability to produce citrullinization of peptides by enzymatic action. 2) Activation of antigenpresenting cells through an effect on TLRs or NLRs. 3) Antigenic mimicry 4) Control of the host immune system (triggering T cell differentiation). 5) Alterations in the permeability of intestinal mucosal. 6) Increase of T helper type 17-mediated mucosal inflammation.

In general, gut microbiome is a double-edged sword. Understanding the mechanism of gut microbiome in RA during pregnancy and lactation will provide potential and effective ideas for controlling the disease activity of RA. Mastering it will be beneficial to the treatment of RA during pregnancy or lactation.

CONCLUSION

In summary, the conclusions of this paper are as follows: 1) Gut microbiome participates in the pathogenesis of RA and plays an important role in the development of RA. 2) There are significant differences in the diversity and abundance of gut microbiome during pregnancy and lactation compared with healthy women. 3) The disease activity of RA fluctuates abnormally during pregnancy or lactation, and the overall manifestation is aggravated, which affects the pregnancy plan. 4) Regulation of gut microbiome during pregnancy or lactation may be an effective treatment for RA. 5) Mechanisms of gut microbiome affecting the disease activity of RA during pregnancy or lactation may be related to the immune system, citrullinization of peptides and permeability of intestinal mucosal.

AUTHOR CONTRIBUTIONS

YY and XC drafted the manuscript. Conceptualization was carried out by YY and CZ. WF assisted in reviewing literature. FR and FW modified the manuscript. FC and XL helped in reviewing the first draft of the manuscript. YY and CZ reviewed and edited the final manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

FUNDING

This study was supported by The National Natural Science Foundation of China (Grant No. 81873838), and Zhejiang Provincial Natural Science Foundation of China (Grant No. LYY18H310001).

REFERENCES

Abdollahi-Roodsaz, S., Abramson, S. B., and Scher, J. U. (2016). The metabolic role of the gut microbiota in health and rheumatic disease: mechanisms and interventions. *Nat. Rev. Rheumatol.* 12 (8), 446–455. doi:10.1038/nrrheum.2016.68

Agorastos, A., and Bozikas, V. P. (2019). Gut microbiome and adaptive immunity in schizophrenia. *Psychiatriki* 30 (3), 189–192. doi:10.22365/jpsych.2019.303.189

Amariuta, T., Luo, Y., Knevel, R., Okada, Y., and Raychaudhuri, S. (2020). Advances in genetics toward identifying pathogenic cell states of rheumatoid arthritis. *Immunol. Rev.* 294 (1), 188–204. doi:10.1111/imr.12827

Angelakis, E., Million, M., Kankoe, S., Lagier, J. C., Armougom, F., Giorgi, R., et al. (2014). Abnormal weight gain and gut microbiota modifications are side effects of long-term doxycycline and hydroxychloroquine treatment. *Antimicrob. Agents Chemother.* 58 (6), 3342–3347. doi:10.1128/AAC.02437-14

Badsha, H. (2018). Role of diet in influencing rheumatoid arthritis disease activity. *Open Rheumatol. J.* 12, 19–28. doi:10.2174/1874312901812010019

Barrett, H. L., Gomez-Arango, L. F., Wilkinson, S. A., McIntyre, H. D., Callaway, L. K., Morrison, M., et al. (2018). A vegetarian diet is a major determinant of gut microbiota composition in early pregnancy. *Nutrients* 10 (7), 890. doi:10.3390/nu10070890

Bermas, B. L. (2017). Lactation and management of postpartum disease. *Rheum. Dis. Clin. N. Am.* 43 (2), 249–262. doi:10.1016/j.rdc.2016.12.002

Bernard, N. J. (2014). Rheumatoid arthritis: Prevotella copri associated with new-onset untreated RA. *Nat. Rev. Rheumatol.* 10 (1), 2. doi:10.1038/nrrheum.2013.187

Biedermann, L., Zeitz, J., Mwinyi, J., Sutter-Minder, E., Rehman, A., Ott, S. J., et al. (2013). Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One* 8 (3), e59260. doi:10.1371/journal.pone.0059260

Bodkhe, R., Balakrishnan, B., and Taneja, V. (2019). The role of microbiome in rheumatoid arthritis treatment. *Ther. Adv. Musculoskelet. Dis.* 11, 1759720X19844632. doi:10.1177/1759720X19844632

Boon, E., Meehan, C. J., Whidden, C., Wong, D. H., Langille, M. G., and Beiko, R. G. (2014). Interactions in the microbiome: communities of organisms and communities of genes. *FEMS Microbiol. Rev.* 38 (1), 90–118. doi:10.1111/1574-6976.12035

Brouwer, J., Hazes, J. M., Laven, J. S., and Dolhain, R. J. (2015a). Fertility in women with rheumatoid arthritis: influence of disease activity and medication. *Ann. Rheum. Dis.* 74 (10), 1836–1841. doi:10.1136/annrheumdis-2014-205383

Brouwer, J., Laven, J. S., Hazes, J. M., and Dolhain, R. J. (2015b). Brief report: miscarriages in female rheumatoid arthritis patients: associations with serologic findings, disease activity, and antirheumatic drug treatment. *Arthritis Rheum.* 67 (7), 1738–1743. doi:10.1002/art.39137

Burmester, G. R., and Pope, J. E. (2017). Novel treatment strategies in rheumatoid arthritis. *Lancet* 389 (10086), 2338–2348. doi:10.1016/S0140-6736(17)31491-5

Cai, X. Y., Zhu, Y., Wang, C., Tang, X. Y., Han, L., Shu, J. L., et al. (2020). Etanercept inhibits B cell differentiation by regulating TNFRII/TRAF2/NF-kappaB signaling pathway in rheumatoid arthritis. *Front. Pharmacol.* 11, 676. doi:10.3389/fphar.2020.00676

Chen, D., Wu, J., Jin, D., Wang, B., and Cao, H. (2019). Fecal microbiota transplantation in cancer management: current status and perspectives. *Int. J. Canc.* 145 (8), 2021–2031. doi:10.1002/ijc.32003

Chen, J., Wright, K., Davis, J. M., Jeraldo, P., Marietta, E. V., Murray, J., et al. (2016). An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. *Genome Med.* 8 (1), 43. doi:10.1186/s13073-016-0299-7

Chen, W. M. Y., Subesinghe, S., Muller, S., Hider, S. L., Mallen, C. D., and Scott, I. C. (2020). The association between gravidity, parity and the risk of developing rheumatoid arthritis: a systematic review and meta-analysis. *Semin. Arthritis Rheum.* 50 (2), 252–260. doi:10.1016/j.semarthrit.2019.09.003

Chen, X., Liu, S., Tan, Q., Shoenfeld, Y., and Zeng, Y. (2017). Microbiome, autoimmunity, allergy, and helminth infection: the importance of the pregnancy period. *Am. J. Reprod. Immunol.* 78 (2). doi:10.1111/aji.12654

Chen, Y., Li, Z., Tye, K. D., Luo, H., Tang, X., Liao, Y., et al. (2019) Probiotic supplementation during human pregnancy affects the gut microbiota and immune status. *Front. Cell Infect. Microbiol.* 9, 254. doi:10.3389/fcimb.2019.00254

Choi, H. H., and Cho, Y. S. (2016). Fecal microbiota transplantation: current applications, effectiveness, and future perspectives. *Clin. Endosc.* 49 (3), 257–265. doi:10.5946/ce.2015.117

Collado, M. C., Isolauri, E., Laitinen, K., and Salminen, S. (2008). Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *Am. J. Clin. Nutr.* 88 (4), 894–899. doi:10.1093/ajcn/88.4.894

Croia, C., Bursi, R., Sutera, D., Petrelli, F., Alunno, A., and Puxeddu, I. (2019). One year in review 2019: pathogenesis of rheumatoid arthritis. *Clin. Exp. Rheumatol.* 37 (3), 347–357.

Crusell, M. K. W., Hansen, T. H., Nielsen, T., Allin, K. H., Ruhlemann, M. C., Damm, P., et al. (2018). Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. *Microbiome* 6 (1), 89. doi:10.1186/s40168-018-0472-x

da Silva, T. F., Casarotti, S. N., de Oliveira, G. L. V., and Penna, A. L. B. (2020). The impact of probiotics, prebiotics, and synbiotics on the biochemical, clinical, and immunological markers, as well as on the gut microbiota of obese hosts. *Crit. Rev. Food Sci. Nutr.*: 1–19. doi:10.1080/10408398.2020.1733483

de Brito Alves, J. L., de Oliveira, Y., Carvalho, N. N. C., Cavalcante, R. G. S., Pereira Lira, M. M., Nascimento, L., et al. (2019). Gut microbiota and probiotic intervention as a promising therapeutic for pregnant women with cardiometabolic disorders: present and future directions. *Pharmacol. Res.* 145, 104252. doi:10.1016/j.phrs.2019.104252

de Jong, P. H., and Dolhain, R. J. (2017). Fertility, pregnancy, and lactation in rheumatoid arthritis. *Rheum. Dis. Clin. N. Am.* 43 (2), 227–237. doi:10.1016/j.rdc.2016.12.004

de Man, Y. A., Dolhain, R. J., van de Geijn, F. E., Willemsen, S. P., and Hazes, J. M. (2008). Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum.* 59 (9), 1241–1248. doi:10.1002/art.24003

de Man, Y. A., Hazes, J. M., van der Heide, H., Willemsen, S. P., de Groot, C. J., Steegers, E. A., et al. (2009). Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum.* 60 (11), 3196–3206. doi:10.1002/art.24914

DeMartino, P., and Cockburn, D. W. (2020). Resistant starch: impact on the gut microbiome and health. *Curr. Opin. Biotechnol.* 61, 66–71. doi:10.1016/j.copbio.2019.10.008

Demoruelle, M. K., and Deane, K. D. (2012). Treatment strategies in early rheumatoid arthritis and prevention of rheumatoid arthritis. *Curr. Rheumatol. Rep.* 14 (5), 472–480. doi:10.1007/s11926-012-0275-1

Di Renzo, G. C., Giardina, I., Clerici, G., Brillo, E., and Gerli, S. (2016). Progesterone in normal and pathological pregnancy. *Horm. Mol. Biol. Clin. Invest.* 27 (1), 35–48. doi:10.1515/hmbci-2016-0038

Doestzada, M., Vila, A. V., Zhernakova, A., Koonen, D. P. Y., Weersma, R. K., Touw, D. J., et al. (2018). Pharmacomicrobiomics: a novel route towards personalized medicine? *Protein Cell* 9 (5), 432–445. doi:10.1007/s13238-018-0547-2

Drago, L. (2019). *Prevotella copri* and microbiota in rheumatoid arthritis: fully convincing evidence? *J. Clin. Med.* 8 (11), 1837. doi:10.3390/jcm8111837

Edwards, S. M., Cunningham, S. A., Dunlop, A. L., and Corwin, E. J. (2017). The maternal gut microbiome during pregnancy. *MCN Am. J. Matern. Child Nurs.* 42 (6), 310–317. doi:10.1097/NMC.0000000000000372

Eiseman, B., Silen, W., Bascom, G. S., and Kauvar, A. J. (1958). Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis. *Surgery* 44 (5), 854–859.

Enright, E. F., Gahan, C. G., Joyce, S. A., and Griffin, B. T. (2016). The impact of the gut microbiota on drug metabolism and clinical outcome. *Yale J. Biol. Med.* 89 (3), 375–382.

Favalli, E. G., Biggioggero, M., Crotti, C., Becciolini, A., Raimondo, M. G., and Meroni, P. L. (2019). Sex and management of rheumatoid arthritis. *Clin. Rev. Allergy Immunol.* 56 (3), 333–345. doi:10.1007/s12016-018-8672-5

Fejzo, M. S., Trovik, J., Grooten, I. J., Sridharan, K., Roseboom, T. J., Vikanes, A., et al. (2019). Nausea and vomiting of pregnancy and hyperemesis gravidarum. *Nat. Rev. Dis. Primers* 5 (1), 62. doi:10.1038/s41572-019-0110-3

Forger, F., and Villiger, P. M. (2016). Treatment of rheumatoid arthritis during pregnancy: present and future. *Expet Rev. Clin. Immunol.* 12 (9), 937–944. doi:10.1080/1744666X.2016.1184973

Franco-de-Moraes, A. C., de Almeida-Pititto, B., da Rocha Fernandes, G., Gomes, E. P., da Costa Pereira, A., and Ferreira, S. R. G. (2017). Worse inflammatory profile in omnivores than in vegetarians associates with the gut microbiota composition. *Diabetol. Metab. Syndrome* 9, 62. doi:10.1186/s13098-017-0261-x

Gerosa, M., Schioppo, T., and Meroni, P. L. (2016). Challenges and treatment options for rheumatoid arthritis during pregnancy. *Expet Opin. Pharmacother.* 17 (11), 1539–1547. doi:10.1080/14656566.2016.1197204

Gohir, W., Whelan, F. J., Surette, M. G., Moore, C., Schertzer, J. D., and Sloboda, D. M. (2015). Pregnancy-related changes in the maternal gut microbiota are dependent upon the mother's periconceptional diet. *Gut Microb.* 6 (5), 310–320. doi:10.1080/19490976.2015.1086056

Gomez, A., Luckey, D., Yeoman, C. J., Marietta, E. V., Berg Miller, M. E., Murray, J. A., et al. (2012). Loss of sex and age driven differences in the gut microbiome characterize arthritis-susceptible 0401 mice but not arthritis-resistant 0402 mice. *PLoS One* 7 (4), e36095. doi:10.1371/journal.pone.0036095

Gomez-Arango, L. F., Barrett, H. L., McIntyre, H. D., Callaway, L. K., Morrison, M., Dekker Nitert, M., et al. (2016a). Connections between the gut microbiome and metabolic hormones in early pregnancy in overweight and obese women. *Diabetes* 65 (8), 2214–2223. doi:10.2337/db16-0278

Gomez-Arango, L. F., Barrett, H. L., McIntyre, H. D., Callaway, L. K., Morrison, M., Dekker Nitert, M., et al. (2016b). Increased systolic and diastolic blood pressure is associated with altered gut microbiota composition and butyrate production in early pregnancy. *Hypertension* 68 (4), 974–981. doi:10.1161/HYPERTENSIONAHA.116.07910

Guerreiro, C. S., Calado, A., Sousa, J., and Fonseca, J. E. (2018). Diet, microbiota, and gut permeability-the unknown triad in rheumatoid arthritis. *Front. Med.* 5, (349. doi:10.3389/fmed.2018.00349

Guo, L. X., Wang, H. Y., Liu, X. D., Zheng, J. Y., Tang, Q., Wang, X. N., et al. (2019). Saponins from *Clematis mandshurica* Rupr. regulates gut microbiota and its metabolites during alleviation of collagen-induced arthritis in rats. *Pharmacol. Res.* 149, 104459. doi:10.1016/j.phrs.2019.104459

Guo, Y., Wang, Z., Chen, L., Tang, L., Wen, S., Liu, Y., et al. (2018). Diet induced maternal obesity affects offspring gut microbiota and persists into young adulthood. *Food Funct.* 9 (8), 4317–4327. doi:10.1039/c8fo00444g

Hasan, S., Aho, V., Pereira, P., Paulin, L., Koivusalo, S. B., Auvinen, P., et al. (2018). Gut microbiome in gestational diabetes: a cross-sectional study of mothers and offspring 5 years postpartum. *Acta Obstet. Gynecol. Scand.* 97 (1), 38–46. doi:10.1111/aogs.13252

Hasegawa, M., Yang, K., Hashimoto, M., Park, J. H., Kim, Y. G., Fujimoto, Y., et al. (2006). Differential release and distribution of Nod1 and Nod2 immunostimulatory molecules among bacterial species and environments. *J. Biol. Chem.* 281 (39), 29054–29063. doi:10.1074/jbc.M602638200

Hudon Thibeault, A. A., Sanderson, J. T., and Vaillancourt, C. (2019). Serotonin-estrogen interactions: what can we learn from pregnancy? *Biochimie* 161, 88–108. doi:10.1016/j.biochi.2019.03.023

Iizumi, T., Battaglia, T., Ruiz, V., and Perez Perez, G. I. (2017). Gut microbiome and antibiotics. *Arch. Med. Res.* 48 (8), 727–734. doi:10.1016/j.arcmed.2017.11.004

Ince-Askan, H., and Dolhain, R. J. (2015). Pregnancy and rheumatoid arthritis. *Best Pract. Res. Clin. Rheumatol.* 29 (4–5), 580–596. doi:10.1016/j.berh.2015.07.001

Ince-Askan, H., Hazes, J. M. W., and Dolhain, R. (2017). Identifying clinical factors associated with low disease activity and remission of rheumatoid arthritis during pregnancy. *Arthritis Care Res.* 69 (9), 1297–1303. doi:10.1002/acr.23143

Jeong, Y., Kim, J. W., You, H. J., Park, S. J., Lee, J., Ju, J. H., et al. (2019). Gut microbial composition and function are altered in patients with early rheumatoid arthritis. *J. Clin. Med.* 8 (5), 693. doi:10.3390/jcm8050693

Jethwa, H., Lam, S., Smith, C., and Giles, I. (2019). Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis. *J. Rheumatol.* 46 (3), 245–250. doi:10.3899/jrheum.180226

Ji, Y. J., Li, H., Xie, P. F., Li, Z. H., Li, H. W., Yin, Y. L., et al. (2019). Stages of pregnancy and weaning influence the gut microbiota diversity and function in sows. *J. Appl. Microbiol.* 127 (3), 867–879. doi:10.1111/jam.14344

Jost, T., Lacroix, C., Braegger, C., and Chassard, C. (2014). Stability of the maternal gut microbiota during late pregnancy and early lactation. *Curr. Microbiol.* 68 (4), 419–427. doi:10.1007/s00284-013-0491-6

Jubair, W. K., Hendrickson, J. D., Severs, E. L., Schulz, H. M., Adhikari, S., Ir, D., et al. (2018). Modulation of inflammatory arthritis in mice by gut microbiota through mucosal inflammation and autoantibody generation. *Arthritis Rheum.* 70 (8), 1220–1233. doi:10.1002/art.40490

Kanerud, L., Scheynius, A., Nord, C. E., and Hafstrom, I. (1994). Effect of sulphasalazine on gastrointestinal microflora and on mucosal heat shock protein expression in patients with rheumatoid arthritis. *Br. J. Rheumatol.* 33 (11), 1039–1048. doi:10.1093/rheumatology/33.11.1039

Kim, D. H. (2015). Gut microbiota-mediated drug-antibiotic interactions. *Drug Metab. Dispos.* 43 (10), 1581–1589. doi:10.1124/dmd.115.063867

Klareskog, L., Padyukov, L., Ronnelid, J., and Alfredsson, L. (2006). Genes, environment and immunity in the development of rheumatoid arthritis. *Curr. Opin. Immunol.* 18 (6), 650–655. doi:10.1016/j.coi.2006.06.004

Konstantinov, S. R., van der Woude, C. J., and Peppelenbosch, M. P. (2013). Do pregnancy-related changes in the microbiome stimulate innate immunity? *Trends Mol. Med.* 19 (8), 454–459. doi:10.1016/j.molmed.2013.06.002

Koren, O., Goodrich, J. K., Cullender, T. C., Spor, A., Laitinen, K., Backhed, H. K., et al. (2012). Host remodeling of the gut microbiome and metabolic changes during pregnancy. *Cell* 150 (3), 470–480. doi:10.1016/j.cell.2012.07.008

Kuang, Y. S., Lu, J. H., Li, S. H., Li, J. H., Yuan, M. Y., He, J. R., et al. (2017). Connections between the human gut microbiome and gestational diabetes mellitus. *GigaScience* 6 (8), 1–12. doi:10.1093/gigascience/gix058

Lamont, R. F. (2015). Advances in the prevention of infection-related preterm birth. *Front. Immunol.* 6, 566. doi:10.3389/fimmu.2015.00566

Lange, K., Buerger, M., Stallmach, A., and Bruns, T. (2016). Effects of antibiotics on gut microbiota. *Dig. Dis.* 34 (3), 260–268. doi:10.1159/000443360

Lee, N., and Kim, W. U. (2017). Microbiota in T-cell homeostasis and inflammatory diseases. *Exp. Mol. Med.* 49 (5), e340. doi:10.1038/emm.2017.36

Lehouritis, P., Cummins, J., Stanton, M., Murphy, C. T., McCarthy, F. O., Reid, G., et al. (2015). Local bacteria affect the efficacy of chemotherapeutic drugs. *Sci. Rep.* 5, 14554. doi:10.1038/srep14554

Li, S., Yu, Y., Yue, Y., Zhang, Z., and Su, K. (2013). Microbial infection and rheumatoid arthritis. *J. Clin. Cell. Immunol.* 4 (6), 174. doi:10.4172/2155-9899.1000174

Li, X., Lu, C., Fan, D., Lu, X., Xia, Y., Zhao, H., et al. (2020). Human umbilical mesenchymal stem cells display therapeutic potential in rheumatoid arthritis by regulating interactions between immunity and gut microbiota via the aryl hydrocarbon receptor. *Front. Cell Dev. Biol.* 8, 131. doi:10.3389/fcell.2020.00131

Lin, H. C., Chen, S. F., Lin, H. C., and Chen, Y. H. (2010). Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study. *Ann. Rheum. Dis.* 69 (4), 715–717. doi:10.1136/ard.2008.105262

Liu, H., Hou, C., Li, N., Zhang, X., Zhang, G., Yang, F., et al. (2019). Microbial and metabolic alterations in gut microbiota of sows during pregnancy and lactation. *FASEB J.* 33 (3), 4490–4501. doi:10.1096/fj.201801221RR

Luckey, D., Gomez, A., Murray, J., White, B., and Taneja, V. (2013). Bugs & us: the role of the gut in autoimmunity. *Indian J. Med. Res.* 138 (5), 732–743.

Maier, L., Pruteanu, M., Kuhn, M., Zeller, G., Telzerow, A., Anderson, E. E., et al. (2018). Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 555 (7698), 623–628. doi:10.1038/nature25979

Malmstrom, V., Catrina, A. I., and Klareskog, L. (2017). The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. *Nat. Rev. Immunol.* 17 (1), 60–75. doi:10.1038/nri.2016.124

Marietta, E., Horwath, I., Balakrishnan, B., and Taneja, V. (2019). Role of the intestinal microbiome in autoimmune diseases and its use in treatments. *Cell. Immunol.* 339, 50–58. doi:10.1016/j.cellimm.2018.10.005

Marietta, E. V., Murray, J. A., Luckey, D. H., Jeraldo, P. R., Lamba, A., Patel, R., et al. (2016). Suppression of inflammatory arthritis by human gut-derived *Prevotella histicola* in humanized mice. *Arthritis Rheum.* 68 (12), 2878–2888. doi:10.1002/art.39785

McHugh, J. (2020). Microbiota-derived metabolites help regulatory B cells suppress arthritis. *Nat. Rev. Rheumatol.* 16 (6), 297. doi:10.1038/s41584-020-0425-1

Meo, S. A., and Hassain, A. (2016). Metabolic physiology in pregnancy. *J. Pakistan Med. Assoc.* 66 (9 Suppl. 1), S8–S10.

Miao, G. P., Zhu, C. S., Feng, J. T., Han, L. R., and Zhang, X. (2015). Effects of plant stress signal molecules on the production of wilforgine in an endophytic actinomycete isolated from Tripterygium wilfordii Hook.f. *Curr. Microbiol.* 70 (4), 571–579. doi:10.1007/s00284-014-0758-6

Mohammed, A. T., Khattab, M., Ahmed, A. M., Turk, T., Sakr, N., , A, M. K., et al. (2017). The therapeutic effect of probiotics on rheumatoid arthritis: a systematic review and meta-analysis of randomized control trials. *Clin. Rheumatol.* 36 (12), 2697–2707. doi:10.1007/s10067-017-3814-3

Morffy Smith, C. D., Gong, M., Andrew, A. K., Russ, B. N., Ge, Y., Zadeh, M., et al. (2019). Composition of the gut microbiota transcends genetic determinants of malaria infection severity and influences pregnancy outcome. *EBioMedicine* 44. 639–655. doi:10.1016/j.ebiom.2019.05.052

Morgan, X. C., Tickle, T. L., Sokol, H., Gevers, D., Devaney, K. L., Ward, D. V., et al. (2012). Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome Biol.* 13 (9), R79. doi:10.1186/gb-2012-13-9-r79

Morovic, W., and Budinoff, C. R. (2020). Epigenetics: a new frontier in probiotic research. *Trends Microbiol.* doi:10.1016/j.tim.2020.04.008

Morrison, D. J., and Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microb.* 7 (3), 189–200. doi:10.1080/19490976.2015.1134082

Mu, Q., Cabana-Puig, X., Mao, J., Swartwout, B., Abdelhamid, L., Cecere, T. E., et al. (2019). Pregnancy and lactation interfere with the response of autoimmunity to modulation of gut microbiota. *Microbiome* 7 (1), 105. doi:10.1186/s40168-019-0720-8

Murakawa, Y. (2016). Pregnancy and lactation in rheumatoid arthritis. *Nihon Rinsho* 74 (6), 1035–1041 [in Japanese].

Mutic, A. D., Jordan, S., Edwards, S. M., Ferranti, E. P., Thul, T. A., and Yang, I. (2017). The postpartum maternal and newborn microbiomes. *MCN Am. J. Matern. Child Nurs.* 42 (6), 326–331. doi:10.1097/NMC.0000000000000374

Nagra, N. S., Robinson, D. E., Douglas, I., Delmestri, A., Dakin, S. G., Snelling, S. J. B., et al. (2019). Antibiotic treatment and flares of rheumatoid arthritis: a self-controlled case series study analysis using CPRD GOLD. *Sci. Rep.* 9 (1), 8941. doi:10.1038/s41598-019-45435-1

Naseer, M., Poola, S., Uraz, S., and Tahan, V. (2020). Therapeutic effects of prebiotics in constipation: a review. *Curr. Clin. Pharmacol.* doi:10.2174/1574884715666200212125035

Nelson, J. L., Voigt, L. F., Koepsell, T. D., Dugowson, C. E., and Daling, J. R. (1992). Pregnancy outcome in women with rheumatoid arthritis before disease onset. *J. Rheumatol.* 19 (1), 18–21.

Neuman, H., Debelius, J. W., Knight, R., and Koren, O. (2015). Microbial endocrinology: the interplay between the microbiota and the endocrine system. *FEMS Microbiol. Rev.* 39 (4), 509–521. doi:10.1093/femsre/fuu010

Neuman, H., and Koren, O. (2017). The pregnancy microbiome. *Nestle Nutr. Inst. Workshop Ser.* 88, 1–9. doi:10.1159/000455207

Ngian, G. S., Briggs, A. M., Ackerman, I. N., and Van Doornum, S. (2016). Safety of anti-rheumatic drugs for rheumatoid arthritis in pregnancy and lactation. *Int. J. Rheum. Dis.* 19 (9), 834–843. doi:10.1111/1756-185X.12860

Norgaard, M., Larsson, H., Pedersen, L., Granath, F., Askling, J., Kieler, H., et al. (2010. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *J. Intern. Med.* 268 (4), 329–337. doi:10.1111/j.1365-2796.2010.02239.x

Nuriel-Ohayon, M., Neuman, H., and Koren, O. (2016). Microbial changes during pregnancy, birth, and infancy. *Front. Microbiol.* 7, 1031. doi:10.3389/fmicb.2016.01031

Nyangahu, D. D., Lennard, K. S., Brown, B. P., Darby, M. G., Wendoh, J. M., Havyarimana, E., et al. (2018). Disruption of maternal gut microbiota during gestation alters offspring microbiota and immunity. *Microbiome* 6 (1), 124. doi:10.1186/s40168-018-0511-7

Ogrendik, M. (2009). Efficacy of roxithromycin in adult patients with rheumatoid arthritis who had not received disease-modifying antirheumatic drugs: a 3-month, randomized, double-blind, placebo-controlled trial. *Clin. Therapeut.* 31 (8), 1754–1764. doi:10.1016/j.clinthera.2009.08.014

Ogrendik, M., and Karagoz, N. (2011). Treatment of rheumatoid arthritis with roxithromycin: a randomized trial. *Postgrad. Med.* 123 (5), 220–227. doi:10.3810/pgm.2011.09.2478

Pahari, S., Chatterjee, D., Negi, S., Kaur, J., Singh, B., and Agrewala, J. N. (2017). Morbid sequences suggest molecular mimicry between microbial peptides and self-antigens: a possibility of inciting autoimmunity. *Front. Microbiol.* ,(1938. doi:10.3389/fmicb.2017.01938

Paysour, M. J., Bolte, A. C., and Lukens, J. R. (2019). Crosstalk between the microbiome and gestational immunity in autism-related disorders. *DNA Cell Biol.* 38 (5), 405–409. doi:10.1089/dna.2019.4653

Pazos, M., Sperling, R. S., Moran, T. M., and Kraus, T. A. (2012). The influence of pregnancy on systemic immunity. *Immunol. Res.* 54 (1–3), 254–261. doi:10.1007/s12026-012-8303-9

Peppercorn, M. A., and Goldman, P. (1972). The role of intestinal bacteria in the metabolism of salicylazosulfapyridine. *J. Pharmacol. Exp. Therapeut.* 181 (3), 555–562.

Peterson, S. N., Bradley, L. M., and Ronai, Z. A. (2020). The gut microbiome: an unexpected player in cancer immunity. *Curr. Opin. Neurobiol.* 62, 48–52. doi:10.1016/j.conb.2019.09.016

Picchianti-Diamanti, A., Panebianco, C., Salemi, S., Sorgi, M. L., Di Rosa, R., Tropea, A., et al. (2018). Analysis of gut microbiota in rheumatoid arthritis patients: disease-related dysbiosis and modifications induced by etanercept. *Int. J. Mol. Sci.* 19 (10), 2938. doi:10.3390/ijms19102938

Pineda Mde, L., Thompson, S. F., Summers, K., de Leon, F., Pope, J., and Reid, G. (2011). A randomized, double-blinded, placebo-controlled pilot study of probiotics in active rheumatoid arthritis. *Med. Sci. Mon. Int. Med. J. Exp. Clin. Res.* 17 (6), CR347–CR354. doi:10.12659/msm.881808

Prakash, O., Shouche, Y., Jangid, K., and Kostka, J. E. (2013). Microbial cultivation and the role of microbial resource centers in the omics era. *Appl. Microbiol. Biotechnol.* 97 (1), 51–62. doi:10.1007/s00253-012-4533-y

Provost, M., Eaton, J. L., and Clowse, M. E. (2014). Fertility and infertility in rheumatoid arthritis. *Curr. Opin. Rheumatol.* 26 (3), 308–314. doi:10.1097/BOR.0000000000000058

Rampelli, S., Candela, M., Turroni, S., Biagi, E., Collino, S., Franceschi, C., et al. (2013). Functional metagenomic profiling of intestinal microbiome in extreme ageing. *Aging (Albany NY)* 5 (12), 902–912. doi:10.18632/aging.100623

Ranjan, R., Rani, A., Metwally, A., McGee, H. S., and Perkins, D. L. (2016). Analysis of the microbiome: advantages of whole genome shotgun versus 16S amplicon sequencing. *Biochem. Biophys. Res. Commun.* 469 (4), 967–977. doi:10.1016/j.bbrc.2015.12.083

Reed, S. D., Vollan, T. A., and Svec, M. A. (2006). Pregnancy outcomes in women with rheumatoid arthritis in Washington state. *Matern. Child Health J.* 10 (4), 361–366. doi:10.1007/s10995-006-0073-3

Reichardt, N., Duncan, S. H., Young, P., Belenguer, A., McWilliam Leitch, C., Scott, K. P., et al. (2014). Phylogenetic distribution of three pathways for propionate production within the human gut microbiota. *ISME J.* 8 (6), 1323–1335. doi:10.1038/ismej.2014.14

Ricke, S. C., Lee, S. I., Kim, S. A., Park, S. H., and Shi, Z. (2020). Prebiotics and the poultry gastrointestinal tract microbiome. *Poultry Sci.* 99 (2), 670–677. doi:10.1016/j.psj.2019.12.018

Rigau-Perez, J. G. (2016). Unlicensed to prescribe herbs: a Chinese healer - medico chino - in Puerto Rico, 1851–1853. *Puert. Rico Health Sci. J.* 35 (2), 100–107.

Roberfroid, M., Gibson, G. R., Hoyles, L., McCartney, A. L., Rastall, R., Rowland, I., et al. (2010). Prebiotic effects: metabolic and health benefits. *Br. J. Nutr.* 104 (Suppl. 2), S1–S63. doi:10.1017/S0007114510003363

Rohr, M. W., Narasimhulu, C. A., Rudeski-Rohr, T. A., and Parthasarathy, S. (2020). Negative effects of a high-fat diet on intestinal permeability: a review. *Adv. Nutr.* 11 (1), 77–91. doi:10.1093/advances/nmz061

Rooks, M. G., and Garrett, W. S. (2016). Gut microbiota, metabolites and host immunity. *Nat. Rev. Immunol.* 16 (6), 341–352. doi:10.1038/nri.2016.42

Round, J. L., Lee, S. M., Li, J., Tran, G., Jabri, B., Chatila, T. A., et al. (2011). The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science* 332 (6032), 974–977. doi:10.1126/science.1206095

Saad, R., Rizkallah, M. R., and Aziz, R. K. (2012). Gut Pharmacomicrobiomics: the tip of an iceberg of complex interactions between drugs and gut-associated microbes. *Gut Pathog.* 4 (1), 16. doi:10.1186/1757-4749-4-16

Santacruz, A., Collado, M. C., Garcia-Valdes, L., Segura, M. T., Martin-Lagos, J. A., Anjos, T., et al. (2010). Gut microbiota composition is associated with body weight, weight gain and biochemical parameters in pregnant women. *Br. J. Nutr.* 104 (1), 83–92. doi:10.1017/S0007114510000176

Savin, Z., Kivity, S., Yonath, H., and Yehuda, S. (2018). Smoking and the intestinal microbiome. *Arch. Microbiol.* 200 (5), 677–684. doi:10.1007/s00203-018-1506-2

Scher, J. U., Sczesnak, A., Longman, R. S., Segata, N., Ubeda, C., Bielski, C., et al. (2013). Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *elife* 2, e01202. doi:10.7554/eLife.01202

Scherer, H. U., Haupl, T., and Burmester, G. R. (2020). The etiology of rheumatoid arthritis. *J. Autoimmun.* 110, 102400. doi:10.1016/j.jaut.2019.102400

Singh, A. (2020). Materials modulate immunity and gut microbiome. *Nat. Mater.* 19 (1), 3–4. doi:10.1038/s41563-019-0557-3

Skoldstam, L., Hagfors, L., and Johansson, G. (2003). An experimental study of a mediterranean diet intervention for patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 62 (3), 208–214. doi:10.1136/ard.62.3.208

Skomsvoll, J. F., Ostensen, M., Irgens, L. M., and Baste, V. (1999). Perinatal outcome in pregnancies of women with connective tissue disease and inflammatory rheumatic disease in Norway. *Scand. J. Rheumatol.* 28 (6), 352–356. doi:10.1080/03009749950155337

Smid, M. C., Ricks, N. M., Panzer, A., McCoy, A. N., Azcarate-Peril, M. A., Keku, T. O., et al. (2018). Maternal gut microbiome biodiversity in pregnancy. *Am. J. Perinatol.* 35 (1), 24–30. doi:10.1055/s-0037-1604412

Sousa, T., Paterson, R., Moore, V., Carlsson, A., Abrahamsson, B., and Basit, A. W. (2008). The gastrointestinal microbiota as a site for the biotransformation of drugs. *Int. J. Pharm.* 363 (1–2), 1–25. doi:10.1016/j.ijpharm.2008.07.009

Sousa, T., Yadav, V., Zann, V., Borde, A., Abrahamsson, B., and Basit, A. W. (2014. On the colonic bacterial metabolism of azo-bonded prodrugsof 5-aminosalicylic acid. *J. Pharm. Sci.* 103 (10), 3171–3175. doi:10.1002/jps.24103

Stanislawski, M. A., Dabelea, D., Wagner, B. D., Sontag, M. K., Lozupone, C. A., and Eggesbo, M. (2017). Pre-pregnancy weight, gestational weight gain, and the gut microbiota of mothers and their infants. *Microbiome* 5 (1), 113. doi:10.1186/s40168-017-0332-0

Sun, Y., Chen, Q., Lin, P., Xu, R., He, D., Ji, W., et al. (2019). Characteristics of gut microbiota in patients with rheumatoid arthritis in shanghai, China. *Front. Cell Infect. Microbiol.* 9, 369. doi:10.3389/fcimb.2019.00369

Tajik, N., Frech, M., Schulz, O., Schalter, F., Lucas, S., Azizov, V., et al. (2020). Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. *Nat. Commun.* 11 (1), 1995. doi:10.1038/s41467-020-15831-7

Teng, F., Klinger, C. N., Felix, K. M., Bradley, C. P., Wu, E., Tran, N. L., et al. (2016). Gut microbiota drive autoimmune arthritis by promoting differentiation and migration of peyer's patch T follicular helper cells. *Immunity* 44 (4), 875–888. doi:10.1016/j.immuni.2016.03.013

The Human Microbiome Project Consortium (2012). Structure, function and diversity of the healthy human microbiome. *Nature* 486 (7402), 207–214. doi:10.1038/nature11234

Vaahtovuo, J., Munukka, E., Korkeamaki, M., Luukkainen, R., and Toivanen, P. (2008). Fecal microbiota in early rheumatoid arthritis. *J. Rheumatol.* 35 (8), 1500–1505.

Vaghef-Mehrabany, E., Alipour, B., Homayouni-Rad, A., Sharif, S. K., Asghari-Jafarabadi, M., and Zavvari, S. (2014). Probiotic supplementation improves inflammatory status in patients with rheumatoid arthritis. *Nutrition* 30 (4), 430–435. doi:10.1016/j.nut.2013.09.007

Van de Wiele, T., Van Praet, J. T., Marzorati, M., Drennan, M. B., and Elewaut, D. (2016). How the microbiota shapes rheumatic diseases. *Nat. Rev. Rheumatol.* 12 (7), 398–411. doi:10.1038/nrrheum.2016.85

van Wattum, J. J., Leferink, T. M., Wilffert, B., and Ter Horst, P. G. J. (2019). Antibiotics and lactation: an overview of relative infant doses and a systematic assessment of clinical studies. *Basic Clin. Pharmacol. Toxicol.* 124 (1), 5–17. doi:10.1111/bcpt.13098

Vande Voorde, J., Sabuncuoglu, S., Noppen, S., Hofer, A., Ranjbarian, F., Fieuws, S., et al. (2014). Nucleoside-catabolizing enzymes in mycoplasma-infected tumor cell cultures compromise the cytostatic activity of the anticancer drug gemcitabine. *J. Biol. Chem.* 289 (19), 13054–13065. doi:10.1074/jbc.M114.558924

Vieira Borba, V., and Shoenfeld, Y. (2019). Prolactin, autoimmunity, and motherhood: when should women avoid breastfeeding? *Clin. Rheumatol.* 38 (5), 1263–1270. doi:10.1007/s10067-018-04415-y

Vindigni, S. M., and Surawicz, C. M. (2017). Fecal microbiota transplantation. *Gastroenterol. Clin. N. Am.* 46 (1), 171–185. doi:10.1016/j.gtc.2016.09.012

Wallenius, M., Skomsvoll, J. F., Irgens, L. M., Salvesen, K. A., Nordvag, B. Y., Koldingsnes, W., et al. (2011). Fertility in women with chronic inflammatory arthritides. *Rheumatology* 50 (6), 1162–1167. doi:10.1093/rheumatology/keq458

Wallenius, M., Skomsvoll, J. F., Irgens, L. M., Salvesen, K. A., Nordvag, B. Y., Koldingsnes, W., et al. (2012). Parity in patients with chronic inflammatory arthritides childless at time of diagnosis. *Scand. J. Rheumatol.* 41 (3), 202–207. doi:10.3109/03009742.2011.641582

Wang, J. W., Kuo, C. H., Kuo, F. C., Wang, Y. K., Hsu, W. H., Yu, F. J., et al. (2019). Fecal microbiota transplantation: review and update. *J. Formos. Med. Assoc.* 118 (Suppl. 1), S23–S31. doi:10.1016/j.jfma.2018.08.011

Weersma, R. K., Zhernakova, A., and Fu, J. (2020). Interaction between drugs and the gut microbiome. *Gut* 69 (8), 1510–1519. doi:10.1136/gutjnl-2019-320204

Weis, M. (2018). Impact of the gut microbiome in cardiovascular and autoimmune diseases. *Clin. Sci. (Lond.)* 132 (22), 2387–2389. doi:10.1042/CS20180410

West, B., Lendrum, R., Hill, M. J., and Walker, G. (1974). Effects of sulphasalazine (Salazopyrin) on faecal flora in patients with inflammatory bowel disease. *Gut* 15 (12), 960–965. doi:10.1136/gut.15.12.960

Wilson, I. D., and Nicholson, J. K. (2017). Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl. Res.* 179, 204–222. doi:10.1016/j.trsl.2016.08.002

Wu, H. J., Ivanov, I. I., Darce, J., Hattori, K., Shima, T., Umesaki, Y., et al. (2010). Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. *Immunity* 32 (6), 815–827. doi:10.1016/j.immuni.2010.06.001

Xiao, M., Fu, X., Ni, Y., Chen, J., Jian, S., Wang, L., et al. (2018). Protective effects of *Paederia scandens* extract on rheumatoid arthritis mouse model by modulating gut microbiota. *J. Ethnopharmacol.* 226, 97–104. doi:10.1016/j.jep.2018.08.012

Yao, Y., Cai, X., Chen, C., Fang, H., Zhao, Y., Fei, W., et al. (2020). The role of microbiomes in pregnant women and offspring: research progress of recent years. *Front. Pharmacol.* 11, 643. doi:10.3389/fphar.2020.00643

Yao, Y., Cai, X., Yu, H., Xu, Q., Li, X., Yang, Y., et al. (2019). PSTPIP2 attenuates joint damage and suppresses inflammation in adjuvant-induced arthritis. *Eur. J. Pharmacol.* 859, 172558. doi:10.1016/j.ejphar.2019.172558

Yao, Y., Yu, H., Liu, Y., Xu, Q., Li, X., Meng, X., et al. (2018). PSTPIP2 inhibits the inflammatory response and proliferation of fibroblast-like synoviocytes *in vitro*. *Front. Pharmacol.* 9, 1432. doi:10.3389/fphar.2018.01432

Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras, M., et al. (2012). Human gut microbiome viewed across age and geography. *Nature* 486 (7402), 222–227. doi:10.1038/nature11053

Young, O. M., Tang, Z., Niven-Fairchild, T., Tadesse, S., Krikun, G., Norwitz, E. R., et al. (2015). Toll-like receptor-mediated responses by placental Hofbauer cells (HBCs): a potential pro-inflammatory role for fetal M2 macrophages. *Am. J. Reprod. Immunol.* 73 (1), 22–35. doi:10.1111/aji.12336

Zeng, Z., Liu, F., and Li, S. (2017). Metabolic adaptations in pregnancy: a review. *Ann. Nutr. Metab.* 70 (1), 59–65. doi:10.1159/000459633

Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., et al. (2015). The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. *Nat. Med.* 21 (8), 895–905. doi:10.1038/nm.3914

Zhou, B., Xia, X., Wang, P., Chen, S., Yu, C., Huang, R., et al. (2018). Induction and amelioration of methotrexate-induced gastrointestinal toxicity are related to immune response and gut microbiota. *EBioMedicine* 33, 122–133. doi:10.1016/j.ebiom.2018.06.029

Zhou, Y., Xu, H., Huang, H., Li, Y., Chen, H., He, J., et al. (2019). Are there potential applications of fecal microbiota transplantation beyond intestinal disorders? *BioMed Res. Int.* 2019 (3469754. doi:10.1155/2019/3469754

Zimmermann, P., and Curtis, N. (2020). Effect of intrapartum antibiotics on the intestinal microbiota of infants: a systematic review. *Arch. Dis. Child. Fetal Neonatal Ed.* 105 (2), 201–208. doi:10.1136/archdischild-2018-316659

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pediatrics

CASE REPORT
published: 24 November 2020
doi: 10.3389/fped.2020.596386

Case Report: Infantile Ischemic Stroke and Antiphospholipid Antibodies, Description of Four Cases

Teresa Giani[1,2], *Angela Mauro*[3], *Giovanna Ferrara*[4*] and *Rolando Cimaz*[5,6]

[1] Azienda Ospedaliera Universitaria Meyer, Florence, Italy, [2] Department of Medical Biotechnology, University of Siena, Siena, Italy, [3] Emergency Department Santobono-Pausilipon Children's Hospital, Naples, Italy, [4] Azienda Unità Sanitaria Locale Toscana Centro, Florence, Italy, [5] Azienda Socio Sanitaria Territoriale G-Pini, Milan, Italy, [6] Department of Clinical Sciences and Community Health and Research Center for Adult and Pediatric Rheumatic Diseases, University of Milan, Milan, Italy

Antiphospholipid syndrome (APS) is a rare condition in childhood, but even more in the neonatal age. Most neonatal cases are considered a passively acquired autoimmune disease, due to a transplacental passage of maternal antiphospholipid antibodies (aPL) from mothers with primary or secondary APS or, more often, from asymptomatic aPL carriers. Exceedingly unusual is the neonatal *de novo* production of aPL. We present four infants with presumed perinatal stroke in presence of increased and persistent aPL levels, even after 6 months of life, opening the window on a gray zone related to the origin of these antibodies (maternal or neonatal) and on their role in the pathogenesis of stroke.

Keywords: APS—antiphospholipid antibody syndrome, perinatal stroke, brain damage, autoimmune disorders, transplacental passage autoantibodies

OPEN ACCESS

Edited by:
Cecilia Beatrice Chighizola, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Sabine Fürst-Recktenwald, Roche, Switzerland
Cristina Tarango, Cincinnati Children's Hospital Medical Center, United States

***Correspondence:**
Giovanna Ferrara
giovanna.ferrara@gmail.com

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pediatrics

Received: *19 August 2020*
Accepted: *28 October 2020*
Published: *24 November 2020*

Citation:
Giani T, Mauro A, Ferrara G and Cimaz R (2020) Case Report: Infantile Ischemic Stroke and Antiphospholipid Antibodies, Description of Four Cases. Front. Pediatr. 8:596386. doi: 10.3389/fped.2020.596386

INTRODUCTION

Anti-phospholipid syndrome (APS), first described in 1986, is an autoimmune disorder characterized by a history of venous or arterial thrombosis and/or of pregnancy morbidity in the presence of persistent anti-phospholipid antibodies (aPL) (1, 2). aPL are a heterogeneous family of autoantibodies including lupus anti-coagulant (LA), anti-cardiolipin antibodies (aCL), and anti-β2-glycoprotein I antibodies (β2GPI) (3). APS can be associated with other autoimmune diseases, mainly with systemic lupus erythematosus, but in many cases can be found in isolation as a primary syndrome (4).

APS commonly develops in adults, especially in young women, while in children it is an unusual condition accounting for $< 3\%$ of the cases (5). In the neonatal age APS is exceedingly rare. Most of the cases are considered a passively acquired autoimmune disease (6). Maternal IgG isotype aPL from mothers with primary or secondary APS or, more often, from asymptomatic aPL carriers can pass into the fetal circulation, actively transported through the placenta (7).

Only few cases have been described in literature of *de novo* aPL production in neonatal age. A negative maternal aPL profile, a prolonged persistence of aPL in offspring, IgM isotypes may help in distinguishing between *de novo* and acquired autoimmunity, which would be useful for prognostic evaluation and supporting the treatment choice.

Maternal APS is known to predispose to prematurity, and intrauterine growth restriction, and to increase the risk of thrombosis, thrombocytopenia, and developmental delay in neonates (8).

Acute ischemic stroke, arterial and venous thrombosis have been observed in neonatal APS, but additional prothrombotic risk factors may be crucial to trigger the final pathological event in these situations (9).

We present four infants with persistent levels of aPL, even after 6 months of life, who developed brain stroke, and discuss the possible origin of aPL, and their role in early ischemic stroke.

Table 1 summarizes the main features of these four cases, which are described in detail below.

CASE 1

A baby boy was born at 38 weeks of gestational age via normal vaginal delivery. The mother, a 25-year-old healthy woman, without previous history of miscarriages, had suffered from mild *abruptio placentae* at 11 weeks of gestation and premature uterine contractions at the 30th week. Routine blood tests during pregnancy were normal, and routine ultrasound scans, the last of which performed 6 weeks before delivery, did not reveal fetal complications. There was no family history for coagulation disorders or vascular events.

Newborn appeared in good general conditions, with APGAR score 9/10 at first and fifth minute, respectively, and weight of 3,450 kg. He was discharged at 48 h of life.

At 10 days of life the baby showed a poor feeding, an asymmetry in the movements and posture with a weak use of his right side, and a preferential attitude of the head to be rotated to the left. At 6 weeks of age the child was brought to the emergency room because of jerking movements of his arms and legs lasting 5–10 min. He appeared hypotonic, with asymmetric Moro reflexes, absence of spontaneous movements of the right limbs, and poor visual alertness. During hospitalization he presented a divergent strabismus, and partial seizures lasting 5–10 min. Results from blood samples, including immune and infection profiles and a routine coagulation study, electrocardiography, and echocardiography were normal. A video-electroencephalogram showed continuous background activity with seizure activity mainly on the left hemisphere.

Magnetic resonance imaging (MRI) of the brain documented in the fronto-parietal-temporal left regions a large pluri-cystic area with altered intensity of signal involving the cortico-subcortical tissues, and extending in depth until the wall of the lateral ventricle, and extensive damages at caudate, striatum, internal and external capsule, thalamus, cerebral peduncle of the midbrain and left hemipons, and bulbar pyramid. The angio-MR revealed a narrowing of the left middle cerebral artery.

A neonatal hypoxic ischemic syndrome was postulated, and an antiepileptic treatment was started with seizure control. At 5 months of age an extensive investigation of prothrombotic risk factors was performed, revealing aCL IgG 45 U/ml (n.v. <12) with negative IgM, anti-β2GPI IgG 60 U/ml (n.v. <12) with negative IgM, and homocysteine level of 19 μmol/L (<15). Furthermore, the child resulted heterozygous for factor V Leiden (FVL) mutation, like his father, while his mother was negative.

A neonatal APS related to possible transplacental passage of maternal IgG antibodies was hypothesized, and low dose aspirin was prescribed.

Antibody testing for autoimmune disorders, and thrombophilia panel including aPL were obtained in his mother 6 months after delivery and resulted all negative or normal, except for a positive ANA result (1:160, speckled).

At 9 months of age the aPL were absent in the child, and aspirin prophylaxis was interrupted.

At last follow-up, at 13 months of age, the patient still appeared hypotonic, with an insufficient head control, a right hemiplegia and a global delay in his psychomotor development.

CASE 2

A female was born at 38 weeks of gestation via normal vaginal delivery from a 34-year-old woman, at her first pregnancy. APGAR score was 10/10 at first and fifth minute, respectively, and birth weight was 2,770 kg. She was discharged 48 h later in good general conditions. The pregnancy was complicated by insulin-controlled maternal gestational diabetes. There was no history of miscarriages or family history of coagulation disorders or vascular events.

When she was 5 months old her parents observed a progressive reduction in the use of their child's left arm. On clinical examination hemiparesis of upper and lower left limbs, and microcephaly were noticed. Electroencephalogram showed an extensively unstructured right rhythm, without clear signs of epilepsy. Cerebral MRI and MR angiography, performed at 6 months of life, revealed a right atrophy of the white matter, basal and thalamic ganglia, and encephalic trunk, with wallerian degeneration of corticospinal bundle, evocating an ischemic event involving the right middle cerebral artery territory supposed to have occurred several months before, presumably during the perinatal period.

At 6 months of age routine laboratory tests were repeated including a thrombophilia risk screen. Increased values of anti-β2GPI IgG (120 U/ml), with negative IgM, and of aCL IgG (20 U/ml), with negative IgM were documented.

Autoimmune panel and thrombophilia panel including aPL were also performed in her mother when the child was 10 months old and all resulted negative except for the presence of low titer ANA (1:80).

Three months later the patient's anti-β2GPI IgG were still present at 118 U/ml, while aCL were absent. IgG β2GPI progressively reduced and disappeared by the age of 16 month.

Being aPL persistently negative in the absence of other prothrombotic risks factors no treatment was started. One year later, following a regular rehabilitation program, the patient's neurologic status showed a satisfactory functional recovery.

CASE 3

A female baby was born at term by elective cesarean section for previous cesarean, without prenatal complications or abnormalities. No postnatal resuscitation was required, APGAR

TABLE 1 | Clinical and laboratory data of the 4 infants.

		Case 1	Case 2	Case 3	Case 4
Prenatal data	Age of the mother at pregnancy	25	34	30	39
	Previous pregnancy related complications	Absent	Absent	2 miscarriages	Absent
	Maternal aPL	Absent	Absent	Anti-β2GPI IgG/IgM: 10/15 U/ml Anti-CL IgG/IgM: 40/46 U/ml LAC IgG/IgM: absent/absent	Absent
Perinatal data	Pregnancy risk factors	*Abruptio placentae* premature uterine contractions	Gestational diabetes	Absent	Gestational diabetes
	Type of delivery	Vaginal	Vaginal	Cesarean section	Cesarean section
	Gestational Age	38+2 w	38 w	39 w	31+6 w
	APGAR score at I and V minute	9–10	10–10	9–9	6–7
	Birth weight	3,450 g	2,770 g	3,600 g	1,350 g
	Perinatal risk factors	Absent	Absent	Absent	Premature rupture of membranes
	Neonate gender	Male	Female	Female	Female
Children	First PAS manifestations	Jerking movements, hypotonia, partial seizures poor spontaneous movements, divergent strabismus	Left hemiparesis	Right hemiparesis	None
	Timing of first PAS manifestations	10 days	5 months	5 months	Radiological signs of cerebral ischemia during perinatal period
	Brain damage area	Left middle cerebral artery territory	Right middle cerebral artery territory	Fronto-temporal-parietal left regions	Fronto-parietal and occipital right regions
	aPL profile	Anti-β2GPI IgG/IgM: 60 U/ml/absent Anti-CL IgG/IgM: 45 U/ml/absent LAC IgG/igM: absent/absent	Anti-β2GPI IgG/IgM: 120 U/ml/absent Anti-CL IgG/IgM: 20 U/ml/absent LAC IgG/IgM: absent/absent	Anti-β2GPI IgG/IgM: 100 U/ml/Absent Anti-CL IgG/IgM: 101 U/ml/Absent LAC IgG/IgM: 52.5 U/ml/Absent	Anti-β2GPI IgG/IgM: 70/35 U/ml Anti-CL IgG/IgM: Absent/absent LAC IgG/IgM: absent/absent
	Age at testing	5 months	6 months	9 months	23 months
	Additional pro-thrombotic factors	Heterozygous for FVL mutation Homocysteine: 19 μmol/L	Absent	D-dimer: 314 ng/ml Protein C: 53% Protein S: 39% Plasminogen: 67% Compound heterozygosis for mutations of MTHFR gene	Absent
	Timing of aPL disappearance	9 months	16 months	20 months	26 months
	Treatment	Aspirin (4 mg/kg/d)	None	Aspirin (4 mg/kg/d)	None
	Outcome	Hypotonia, right hemiplegia, delay psychomotor development	Mild neurological impairment	Left hemiparesis	Complete recovery

aPL, antiphospholipid antibodies; LA, lupus anticoagulant; aCL, anti-cardiolipin antibodies; β2GPI, anti-β2-glycoprotein I antibodies; PAS, perinatal arterial ischemic stroke. Normal values, nv; Anti-β2GPI, IgG<12U/ml; IgM <12 U/ml; Anti-CL, IgG <12 U/ml; IgM <10 U/ml; Homocysteine, <15 μmol/L.

score was 9 /9 at first and fifth minute, respectively, and birth weight 3,600 kg.

The mother, a 30-year-old woman with vitiligo, reported 2 previous miscarriages: the first at 9 weeks of gestation, the second at 12 weeks. In this last occasion a screening for aPL was performed revealing aCL IgM 38 U/ml, IgG 30 U/ml, anti-β2GPI IgM 20 U/ml, and IgG 20 U/ml. She denied any previous thrombotic events.

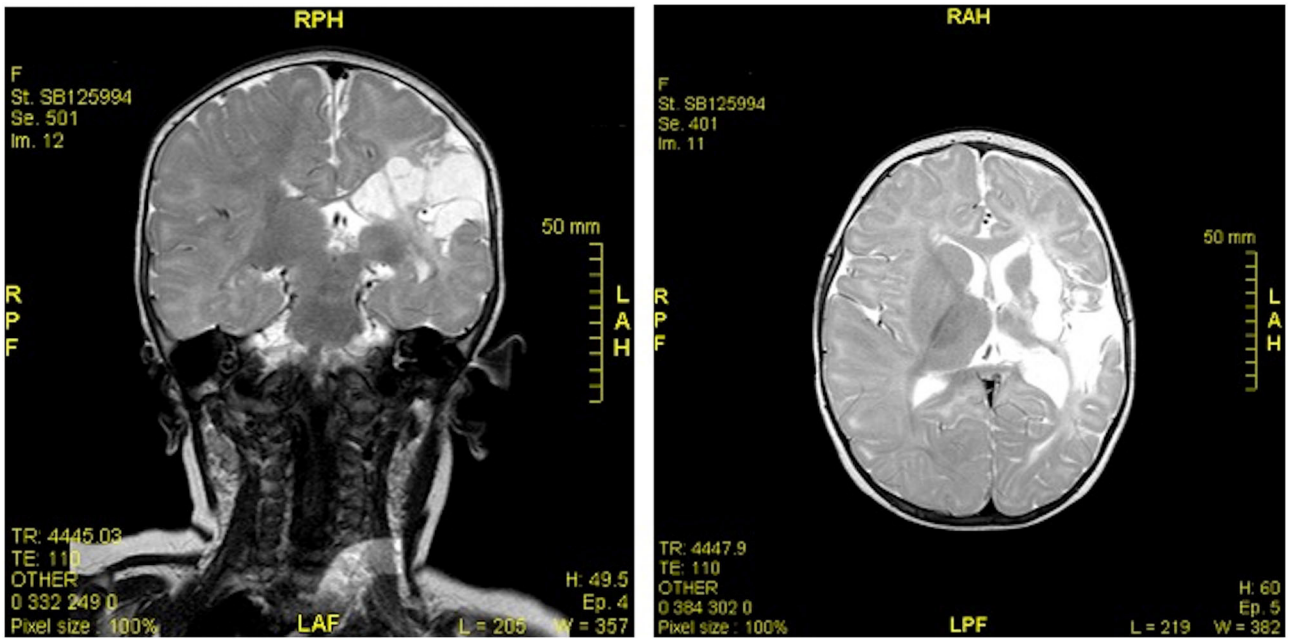


FIGURE 1 | MR imaging (coronal and axial sections) showed ex-vacuo left ventricular dilatation and a cortico-subcortical fronto-temporal-parietal left malacia extending to the ipsilateral capsular regions and to the basal ganglia, without the involvement of the head of the caudate nucleus or the thalamus.

At 5 months of age her parents began to notice a reduced use of her right arm. A neurological evaluation confirmed a right-side hemiparesis.

Blood tests and coagulation studies were ordered including full blood count, urea and electrolytes, liver function tests, coagulation profile, and D-dimer and all resulted within the normal limits.

The EEG recorded abnormal left hemisphere electrogenesis. The CT scan identified a cortico-subcortical left fronto-parietal extended malacic area. MR imaging showed ex-vacuo left ventricular dilatation and a cortico-subcortical fronto-temporal-parietal left malacia extending to the ipsilateral capsular regions and to the basal ganglia, without the involvement of the head of the caudate nucleus or the thalamus (**Figure 1**). A perinatal hypoxic-ischemic damage was supposed, and a physiotherapy treatment was started to promote recovery.

At 9 months of age the child was referred to our hospital for a second opinion. On physical examination, a mild right hemiparesis with decreased muscle strength was observed. A full thrombophilia screen was required and laboratory tests resulted in normal range/negative except for: D-Dimer (314 ng/ml, normal range <250), protein C (53%, normal range 70–140), protein S (39%, normal range 54–124), plasminogen (67%, normal range 80–120), aCL IgG 101 U/ml, IgM negative, anti-β2GPI IgG >100 U/ml, and IgM negative. A compound heterozygosis for the C677T and A1298C mutations of the methylenetetrahydrofolate reductase (MTHFR) gene was detected. Mother's serological examinations, performed when the child was 10 months old, showed aCL IgG 40 U/ml, IgM 46 U/ml, and anti-β2GPI IgG 10 U/ml, IgM 15 U/ml.

Treatment with baby aspirin was prescribed, and a physical and occupational therapy program were recommended. aPL were periodically checked and disappeared after 20 months of age. At last follow-up, at the age of 3 years, the child appeared in good general conditions with persistent, mild neurologic outcome.

CASE 4

A 22-month-old female infant presented to our attention for a 1-month history of skin color changes. The distal extremities of her hands, sometimes also of her feet and tongue, dramatically changed from white to blue discoloration upon exposure to cold.

The baby was born from a dichorionic-diamniotic twin pregnancy complicated at the 25th week with gestational diabetes. The mother was a previously healthy 39-year-old primigravida. She was the first-born twin after an emergency cesarean section, required at the 31st week due to uterine contractions and rupture of membranes. The APGAR score was 6 and 7 at first and fifth minutes, respectively; birth weight was 1,350 g. She received resuscitation procedures, including intubation because of respiratory distress and bradycardia. She was admitted to the neonatal intensive care unit where she received surfactant, and mechanical ventilation, then needed oxygen for 21 days.

She was discharged about 3 months later, but despite a normal neurological exam and an adequate psychomotor development she underwent several cerebral echographies in the first year of life due to her prematurity. White matter hyperechogenicity in the periventricular and subcortical area of the right parietal lobe,

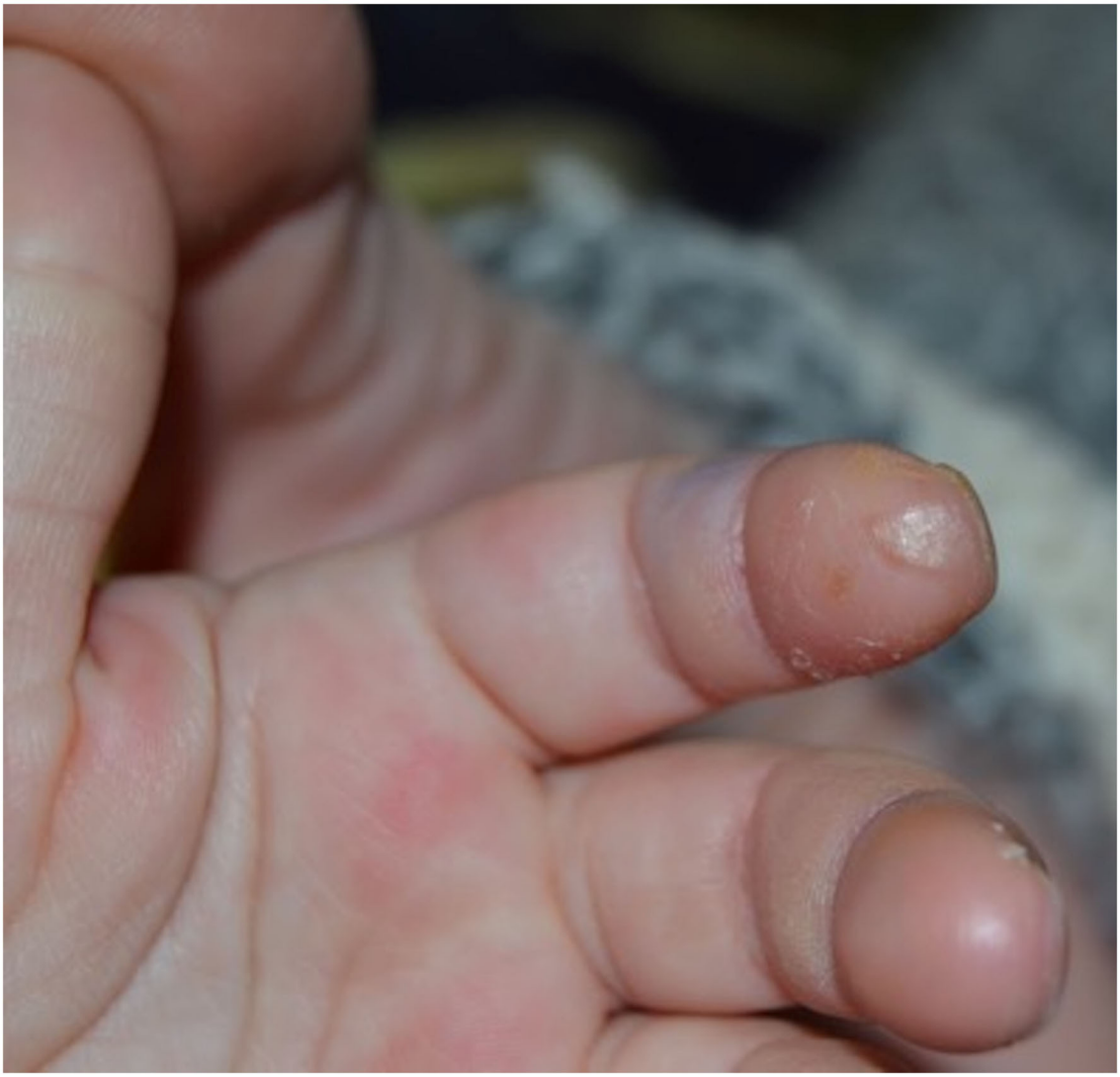


FIGURE 2 | White scar over the tip of the second finger of the right hand derived from a long-lasting ulcerative lesion.

and bilateral periventricular hyperechoic zones at the occipital lobe were detected.

When she came to our attention she appeared in good general conditions with a normal neurological exam. A white pitting scar over the tip of the second finger of the right hand was observed (**Figure 2**). Screening investigations for inherited thrombophilia revealed anti-β2GPI IgG 70 U/ml, and IgM 35 U/ml.

MRI showed a cystic encephalomalacia at the right frontal circumference of the cortical-subcortical site with cortical thinning, mild ventricular dilatation, mild white matter damage near the corona radiata and in the periventricular frontal area.

Mother was promptly tested for autoimmunity, with negative results including aPL. We followed the baby for 2 years. Acrocyanosis gradually resolved within 6 months from the first visit, and anti-β2GPI antibodies disappeared, at 26 months of age.

DISCUSSION

Ischemic stroke has been reported to be the presenting condition in more than a quarter of pediatric patients with APS, as resulted from a multi-national childhood APS registry comprising 121 subjects, including both primary and secondary forms. However, the real impact of APS in the neonatal stroke is unclear (5).

On the other hand, cerebral stroke in neonatal-perinatal period encompasses heterogeneous conditions leading to focal neurological injuries (10). Perinatal arterial ischemic stroke (PAS) is defined as a focal (or multifocal) cerebral ischemic infarction, confirmed by radiological or pathological assessment, due to an arterial event, and occurring between 28 weeks' gestation and 28 days of postnatal age. The incidence of perinatal stroke has been estimated at about 1:3,000–4,000 live births (11).

Perinatal stroke may present acutely in the first week of life with clear neurological symptoms such as seizures, lethargy, apnea and/or poor feeding. However, around 40% of cases are clinically asymptomatic until several months of age, the so called "presumed perinatal strokes" (12–14).

Almost half of perinatal strokes cause a neurological deficit. PAS is the main event responsible for severe outcomes such as neurological disabilities, epilepsy, cognitive impairment (15).

The pathophysiology of perinatal stroke is complex and includes different, possible causes. Risk factors may be related both to maternal and placental conditions, as well as to fetal and neonatal disorders. Maternal preeclampsia, chorioamnionitis, fetal cardiac anomalies, polycythemia, birth asphyxia, and systemic infection are typically described in PAS.

The way genetic and acquired thrombophilic factors act in causing PAS is quite controversial and not completely understood (16).

Simchen et al. (17) investigated the role of maternal and infant prothrombotic factors in a cohort of infants with a history of PAS and their mothers, concluding that both maternal and infant thrombophilia may predispose to PAS. In this study at least one thrombophilic marker was documented in 64% of children, and among 68% of mothers. FVL, protein C deficiency, and aPL prevailed among infants, in particular, more than one-fifth of PAS infants resulted positive for aPL, compared to 5.4% of controls. Almost one-third of mothers resulted positive for FVL, and 18.2% them had aPL (vs. 4.7% of control mothers) (17).

Only part of newborns born to aPL-positive women really acquire aPL antibodies. Data from the European neonatal registry regarding 141 babies born to aPL-positive mothers revealed a low transmission rate (20, 25 and 43%, respectively, for LA, aCL and anti-β2GP1) and no cases of PAS This is in part linked to a filtering effect exerted by placenta through the β2GP1 on trophoblasts membrane, that significantly reduces maternal antibodies transfer (18).

After birth, transmitted antibodies usually disappear within the first months of life (19).

However, also in presence of neonatal antibodies the related manifestations are exceedingly rare, being aPL unable to induce a thrombotic process in the absence of an additional thrombophilic factors (20). Hereditary and/or acquired prothrombotic conditions such as asphyxia, sepsis, dehydration, arterial and venous catheters may contribute to trigger the ischemic event. Therefore, aPL act as a predisposing factor for PAS, in presence of which a thrombophilic screening should be considered (21).

We described four cases of presumed perinatal strokes, as all babies seemed neurologically normal in the neonatal period and up to 28 days post-partum.

Three out of the four children we described (cases 1, 2, and 3) had aPL IgG isotypes, but only one of the paired mothers tested positive (for both aCL and anti-β2GP1). The other two women resulted negative but were tested 6 months after birth, so a transient aPL positivity during pregnancy cannot be excluded. In these children aPL disappeared within 2 years of life (at 6, 16 e 20 months, respectively); we hypothesize an acquired APS due to transplacental autoantibody passage on the basis of the depletion of IgG aPL, and the absence of IgM antibodies. In two of these subjects a predisposing prothrombotic risk factor, as the heterozygosity for factor V Leiden in case 1, and low levels of protein C and S combined to the compound heterozygosity for MTHFR in case 3, had been identified. The exact timing of the ischemic event, as well as the significance of *abruptio placentae* and preterm contractions as predisposing prothrombotic conditions in case 1 remains uncertain.

Case 4 clearly shows a predisposing condition for PAS, being a preterm twin with a perinatal history of resuscitation and ventilation. This baby presented IgM isotypes of anti-β2GP1 antibodies, and her mother tested negative for aPL suggesting a *de novo* APS type. Distinguishing maternally transmitted from *de novo* neonatal APS may be helpful to define the prognosis and to manage the treatment and the follow-up. *De novo* APS may be associated with signs and symptoms (22), such as thrombocytopenia and skin manifestations (i.e., livedo reticularis and Raynaud's phenomenon), which we observed in our case 4. We think that also peripheral ischemia and ulcerative lesions were favored by the thrombophilia due to the presence of aPL, and indeed with the disappearance of these antibodies skin manifestations did not recur.

Most of the neonatal *de novo* APS cases present a multiple aPL positivity, and have a prolonged persistence of antibody titers, while in the acquired type antibodies decline and disappear by 6–12 months (23–25).

Diagnosis of *de novo* neonatal APS is often delayed with a mean time of 4.7 months, probably due to a low awareness of this condition among clinicians, while maternally transmitted APS has been shown to be identified earlier (26).

At the present time, it is still unclear whether outcomes for *de novo* and transmitted neonatal APS are different, and whether the *de novo* APS may precede other autoimmune diseases, such as systemic lupus erythematosus (26–34).

Being a retrospective case series, our report has some limitations: the timing of aPL testing in mother and infant varied and was not followed at same intervals; moreover, none of the children had testing completed at the time of the stroke since they became symptomatic several months after the event. However, pediatric APS is rare and data is lacking in neonatal APS, particularly in cases that may represent primary APS. Our paper is unique in that these infants' mothers were otherwise healthy without known APS or rheumatologic disease and we found elevated antiphospholipid antibodies in the children only since we looked for them.

In conclusion, neonatal APS is a rare hypercoagulation disorder that can predispose to early acute ischemic stroke. The detection of aPL has to be included in the thrombophilic screening in infants who experience a cerebral event, especially when the timing of the stroke is not known like in our cases, even in the absence of a maternal history suggestive for APS or autoimmune disorders. Screening for additional congenital and acquired prothrombotic risk factors should also always be performed in such cases as recommended in the last guidelines for the management of stroke in children (35). The absence of antibodies in the mothers does not rule out the diagnosis of APS in a newborn, since even if rare a *de novo* production of autoantibodies cannot be excluded.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

All authors contributing to the writing of the manuscript, critical review, and accepted the final version.

REFERENCES

1. Hughes GR, Harris NN, Gharavi AE. The anticardiolipin syndrome. *J Rheumatol*. (1986) 13:486–9.
2. Madison JA, Zuo Y, Knight JS. Pediatric antiphospholipid syndrome. *Eur J Rheumatol*. (2019) 7:1–10. doi: 10.5152/eurjrheum.2019.19160
3. Triplett DA. Antiphospholipid antibodies. *Clin Adv Hematol Oncol*. (2003) 1:726–30. doi: 10.1043/0003-9985(2002)126<1424:AA>2.0.CO;2
4. Azarsiz E, Eman G, Akarcan SE, Severcan EU, Karaca N, Aksu G, et al. Anti-β2 Glycoprotein I antibodies in children with rheumatologic disorders. *Indian J Clin Biochem*. (2019) 34:95–100. doi: 10.1007/s12291-017-0711-0
5. Avcin T, Cimaz R, Silverman ED, Cervera R, Gattorno M, Garay S, et al. Pediatric antiphospholipid syndrome: clinical and immunologic features of 121 patients in an international registry. *Pediatrics*. (2008) 122:e1100–e7. doi: 10.1542/peds.2008-1209
6. Da Costa Peixoto MV, de Carvalho JF, Rodrigues CE. Clinical, laboratory, and therapeutic analyses of 21 patients with neonatal thrombosis and antiphospholipid antibodies: a literature review. *J Immunol Res*. (2014) 2014:672603. doi: 10.1155/2014/672603
7. Motta M, Chirico G, Biasini Rebaioli C, Faden D, Lojacono A, Allegri F, et al. Anticardiolipin and anti-beta2 glycoprotein I antibodies in infants born to mothers with antiphospholipid antibody-positive autoimmune disease: a follow-up study. *Am J Perinatol*. (2006) 23:247–51. doi: 10.1055/s-2006-939533
8. Cho A, Hsieh S, Su Y, Jen S, Chen C, Chou H, et al. Neonatal and pregnancy outcome in primary antiphospholipid syndrome: a 10-year experience in one medical center. *Pediatr Neonatol*. (2009) 50:143–6. doi: 10.1016/S1875-9572(09)60052-8
9. Chalmers EA. Perinatal stroke—risk factors and management. *Br J Haematol*. (2005) 130:333–43. doi: 10.1111/j.1365-2141.2005.05554.x
10. Lynch JK, Nelson KB. Epidemiology of perinatal stroke. *Curr Opin Pediatr*. (2001) 13:499–505. doi: 10.1097/00008480-200112000-00002
11. Martinez-Biarge,M, Ferriero DM, Cowan FM. Perinatal arterial ischemic stroke. *Handb Clin Neurol*. (2019) 162:239–66. doi: 10.1016/B978-0-444-64029-1.00011-4
12. Basu AP. Early intervention after perinatal stroke: Opportunities and challenges. Almost half of perinatal strokes causes a neurological deficit. *Dev Med Child Neurol*. (2014) 56:516–21. doi: 10.1111/dmcn.12407
13. Golomb MR, MacGregor DL, Domi T, Armstrong DC, McCrindle BW, Mayank S, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol*. (2001) 50:163–8. doi: 10.1002/ana.1078
14. Sreenan C, Bhargava R, Robertson CM. Cerebral infarction in the term newborn: clinical presentation and long-term outcome. *J Pediatr*. (2000) 137:351–5. doi: 10.1067/mpd.2000.107845
15. Soybilgic A, Avcin T. Pediatric APS: state of the art. *Curr Rheumatol*. (2020) 22:9. doi: 10.1007/s11926-020-0887-9
16. Li C, Miao JK, Xu Y, Hua YY, Ma Q, Zhou LL, et al. Prenatal, perinatal and neonatal risk factors for perinatal arterial ischaemic stroke: a systematic review and meta-analysis. *Eur J Neurol*. (2017) 24:1006–15. doi: 10.1111/ene.13337
17. Simchen MJ, Goldstein G, Lubetsky A, Strauss T, Schiff E, Kenet G. Factor V Leiden and antiphospholipid antibodies in either mothers or infants increase the risk for perinatal arterial ischemic stroke. *Stroke*. (2009) 40:65–70. doi: 10.1161/STROKEAHA.108.527283
18. Motta M, Boffa MC, Tincani A, Avcin T, De Carolis S, Lachassine E. Follow-up of babies born to mothers with antiphospholipid syndrome: preliminary data from the European neonatal registry. *Lupus*. (2012) 21:761–3. doi: 10.1177/0961203312446387
19. Berkun Y, Simchen MJ, Strauss T, Menashcu S, Padeh S, Kenet G. Antiphospholipid antibodies in neonates with stroke–a unique entity or variant of antiphospholipid syndrome? *Lupus*. (2014) 23:986–93. doi: 10.1177/0961203314531842
20. Boffa MC, Lachassinne E. Infant perinatal thrombosis and antiphospholipid antibodies: a review. *Lupus*. (2007) 16:634–41. doi: 10.1177/0961203307079039
21. Nelson KB. Perinatal ischemic stroke. *Stroke*. (2007) 38:742–5. doi: 10.1161/01.STR.0000247921.97794.5e
22. Motta M, Rodriguez-Perez C, Tincani A, Lojacono A, Nacinovich R, Chirico G. Neonates born from mothers with autoimmune disorders. *Early Hum Dev*. (2009) 85:S67–70. doi: 10.1016/j.earlhumdev.2009.08.020
23. Antonvic A, Sennström M, Bremme K, Svenungsson E. Obstetric antiphospholipid syndrome. *Lupus Sci Med*. (2018) 5:e000197. doi: 10.1136/lupus-2016-000197
24. Bhat MA, Kawoosa MS, Bhat JI, Ali SW. Antiphospholipid syndrome in a neonate. *Pediatr Dermatol*. (2011) 28:342–5. doi: 10.1111/j.1525-1470.2010.01254.x
25. Berkun Y, Padeh S, Barash J, Uziel Y, Harel L, Mukamel M, et al. Antiphospholipid syndrome and recurrent thrombosis in children. *Arthritis Rheum*. (2006) 55:850–5. doi: 10.1002/art.22360
26. Gordon O, Almagor Y, Fridle D, Mandel A, Qutteineh H, Yanir A, et al. *De novo* neonatal antiphospholipid syndrome: a case report and review of the literature. *Semin Arthritis Rheum*. (2014) 44:241–5. doi: 10.1016/j.semarthrit.2014.04.003
27. Paro-Panja D, Kitanovski L, Avcin T. Neonatal antiphospholipid syndrome associated with heterozygous methylentetrahydrofolate reductase C677T and prothrombin G20210A gene mutations. *Rheumatology*. (2007) 46:720–1. doi: 10.1093/rheumatology/kem011
28. De Carolis MP, Salvi S, Bersani I, De Carolis S. Isolated cerebral sinovenous thrombosis: a rare case of neonatal antiphospholipid syndrome. *Indian Pediatr*. (2012) 49:411–2.
29. Ebeling F, Petäjä J, Alanko S, Hirvasniemi A, Holm T, Lahde M, et al. Infant stroke and beta-2-glycoprotein1 antibodies: sixcases. *Eur J Pediatr*. (2003) 162:678–81. doi: 10.1007/s00431-003-1285-9
30. Rego Sousa P, Figueira R, Vasconcellos R. Neonatal stroke associated with *de novo* antiphospholipid antibody and homozygous 1298C/C methylene tetrahydrofolate reductase mutation. *BMJ Case Rep*. (2012) 2012:bcr2012006451. doi: 10.1136/bcr-2012-006451
31. Cabral M, Abadesso C, Conde M, Almeida H, Carreiro H. Catastrophic antiphospholipid syndrome: first signs in the neonatal period. *Eur J Pediatr*. (2011) 170:1577–83. doi: 10.1007/s00431-011-1548-9
32. Alshekaili J, Reynolds G, Cook MC. *De novo* infantile primary antiphospholipid antibody syndrome. *Lupus*. (2010) 19:1565–8. doi: 10.1177/0961203310375263

33. Soares Rolim AM, Castro M, Santiago MB. Neonatal antiphospholipid syndrome. *Lupus*. (2006) 15:301–3. doi: 10.1191/0961203306lu2295cr
34. Merlin E, Doré E, Chabrier S, Biard M, Marques-Verdier A, Stéphan JL. A case of infantile *de novo* primary antiphospholipid syndrome revealed by a neonatal arterial ischemic stroke. *J Child Neurol*. (2012) 27:1340–2. doi: 10.1177/0883073811435238
35. Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, et al. Management of stroke in neonates and children: a scientific statement from the American Heart Association/American Stroke Association. *Stroke*. (2019) 50:e51–96. doi: 10.1161/STR.0000000000000183

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

BRIEF RESEARCH REPORT
published: 10 December 2020
doi: 10.3389/fphar.2020.604866

IL-6 but Not TNFα Levels Are Associated With Time to Pregnancy in Female Rheumatoid Arthritis Patients With a Wish to Conceive

Margot Bongenaar, Hieronymus T. W. Smeele, Erik Lubberts and Radboud J. E. M. Dolhain*

Department of Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands

Fertility issues are common amongst women with rheumatoid arthritis (RA). Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα), known key players in RA pathogenesis, have been associated with reproductive disorders. This study investigates the role of these cytokines in decreased fertility in women with active RA. Preconception cytokine measurements of 61 patients from the PARA-cohort, a prospective study on RA and pregnancy, were studied in relation to time to pregnancy as a measure for fertility. IL-6 levels were higher in patients with a time to pregnancy longer than 1 year (p = 0.016). Survival analysis of patients stratified by high or low serum IL-6 levels, shows a prolonged time to pregnancy in the high IL-6 group (p = 0.045). Univariate cox regression analysis of IL-6 in relation to time to pregnancy as well as multivariate cox regression analysis correcting for age, disease activity, nulliparity, NSAID use and prednisone use were performed, with hazards ratios for log transformed IL-6 of 0.68 (95% CI: 0.51–0.93, p = 0.015) and 0.66 (95% CI: 0.43–0.99, p = 0.044), respectively. For TNFα, no association with time to pregnancy was found. This study shows that high IL-6, but not TNFα, is associated with decreased fertility in women with RA. This finding provides a rationale to therapeutically target the IL-6 pathway in the time period before pregnancy. More research in the form of large cohort studies on drug safety and the effect of bDMARDS on fertility is needed for implementation of treatment strategies directed at fertility issues in women with RA.

Keywords: rheumatoid arthritis, interleukin 6, pregnancy, fertility, BDMARDs (biologic agents)

OPEN ACCESS

Edited by:
Maria Gerosa,
University of Milan, Italy

Reviewed by:
Meina Tao Tang,
Genentech, Inc., United States
Carrie A. Vyhlidal,
Children's Mercy Hospital,
United States

****Correspondence:***
Margot Bongenaar
m.bongenaar@erasmusmc.nl

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *10 September 2020*
Accepted: *19 November 2020*
Published: *10 December 2020*

Citation:
Bongenaar M, Smeele HTW, Lubberts E and Dolhain RJ EM (2020) IL-6 but Not TNFα Levels Are Associated With Time to Pregnancy in Female Rheumatoid Arthritis Patients With a Wish to Conceive. Front. Pharmacol. 11:604866. doi: 10.3389/fphar.2020.604866

INTRODUCTION

During reproductive age, rheumatoid arthritis (RA) is one of the most common chronic diseases. Female patients with RA have more difficulty conceiving a child, reflected by higher subfertility rates, longer time to pregnancy and decreased family size (Smeele and Dolhain, 2019). Subfertility, defined as a time to pregnancy of greater than 12 months, is related to disease activity in RA patients (Brouwer et al., 2015). Therefore, underlying immunological pathogenic factors associated with active disease are thought to be involved. To date, immunologic mechanisms causing subfertility in RA patients remain unresolved. Identifying which factors influence fertility may have implications on how to optimally treat women with RA and a wish to conceive.

Two well-known factors contributing to RA pathogenesis are interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) (Yoshida and Tanaka, 2014; Smolen et al., 2016). In normal physiology, IL-6 and TNFα both act as mediators of the acute phase response. In RA, persistent expression of IL-6 contributes to synovial inflammation and damage and is involved in T-cell migration and activation (Tanaka et al., 2014; McInnes and Schett, 2017). Dysregulation of TNFα in RA plays a major role in synovial proliferation and the pro-inflammatory signaling cascade in the joint. Therapies targeting the IL-6 receptor and TNFα are effective treatment options for RA patients (Taylor and Feldmann, 2009; Kang et al., 2019).

Next to their roles in RA pathogenesis, IL-6 and TNFα play a role in reproduction physiology. Dysregulation of IL-6, up or down, may impair fertility and harm pregnancy (Markert et al., 2011). IL-6 has been described to play a role in several inflammatory disorders of the female reproductive organs. For example in endometriosis, serum IL-6 levels are increased in patients and high levels of IL-6 in peritoneal fluid are linked to infertility (Wang F. et al., 2018; Wang X. M. et al., 2018). Likewise, in polycystic ovary syndrome (PCOS), IL-6 levels are higher than in matched controls and a positive correlation between high circulating IL-6 levels and androgen status was described (Peng et al., 2016). Moreover, serum IL-6 levels are higher in women with unexplained infertility (Demir et al., 2009). To a lesser extent, similar associations for TNFα and reproductive disorders are reported: like IL-6, TNFα is increased in endometriosis and PCOS patients (Iwabe et al., 2002; Wu and Ho, 2003; Ebejer and Calleja-Agius, 2013).

The roles of IL-6 and TNFα in subfertility of RA patients are yet unknown. Unraveling the role of these cytokines in subfertile RA patients might open the door to new treatment strategies. Taking above-stated information into account, we hypothesize that high levels of circulating IL-6 and TNFα in women with active RA contribute to subfertility in these patients.

METHODS

Study Population

This study is embedded in the Pregnancy-induced Amelioration of RA (PARA) study, a prospective nationwide cohort of pregnant women with RA in the Netherlands (2002–2010) that previously has been extensively described in literature (de Man et al., 2008). Patients fulfilling the 1987 American College of Rheumatology criteria for RA (Arnett et al., 1988) with a wish to conceive or who were already pregnant were included. After completion of the PARA study, patients who gave permission to be contacted for future research were approached to participate in a follow-up study. In this follow-up study, patients filled in questionnaires including inquiries on their reproductive history, mode of conception for each pregnancy, visits to a gynecologist, fertility assessments and fertility treatments. These studies were approved by the Erasmus MC medical ethics review board and was executed in compliance with the Helsinki Declaration. All patients were above 18 years of age and gave a written informed consent.

Data Collection

In the PARA study, home visits were performed before, three times during and three times after pregnancy. The visit before conception took place if the patient had a desire to conceive and she and her partner did not use any contraceptives. If a patient did not conceive within a year after the first visit, another visit took place. At first visit, data on patient and disease characteristics were collected, as well as medical and obstetric history. At each visit, a physical exam was performed and disease activity was scored using the 28-joint disease Activity Score with three variables based on the C-reactive protein (CRP) level (DAS28-CRP) according to literature (Fransen and van Riel, 2009). CRP was determined using the Tina-Quant CRP Immunological Test System (Roche Diagnostics, Almere, The Netherlands).

Additionally, blood samples were collected and serum was stored at −80°C until use. IL-6 and TNFα serum levels were measured using the IMMULITE 1000 (Siemens Healthcare Diagnostics, Breda, The Netherlands). The intra-run/inter-run mean ± variation coefficient was 105.6 ± 4.9%/87.67 ± 6.1% for IL-6 and 105.6 ± 4.9%/89.5 ± 3.8% for TNFα, with a detection threshold of 2.0 pg/ml. All cytokine levels are presented in pg/ml. Cytokine levels represent the same data as previously described by de Steenwinkel et al. (2013). In that study, the effect of circulating maternal cytokines on birth weight of children was studied at several time points during pregnancy. Measurements were performed on serum taken at the preconception visit as an estimate for cytokine levels during early pregnancy. In this paper, preconception cytokine levels were re-analyzed in relation to time to pregnancy. Therefore, the patients studied represent a subgroup of the patients in the PARA-study: a pre-pregnancy serum should be available and the patients should have given birth during the follow-up period of the study.

Time to Pregnancy Calculation

Time to pregnancy was calculated as described by Brouwer et al. (2015). At the preconception visit, the date the patient first began trying to conceive actively was noted. Time to pregnancy was calculated as the time elapsed between the first attempt to conceive and the first day of the last menstrual period before pregnancy. If the date of the last menstrual period was not known by the patient, this date was calculated by subtracting 280 days (40 weeks) from the due date based on sonographic examination during early pregnancy. Because in several cases the couple succeeded within the first month of trying to conceive, we calculated a fictitious date by adding 28 days to the start of the last menstrual period for all patients to avoid negative time to pregnancy values.

Statistical Analysis

Descriptive statistics are presented as mean (SD), number (percentage) or median [interquartile range (IQR)]. Characteristics of study population subgroups stratified by time to pregnancy longer or shorter than 1 year were compared using two-sample t tests, Wilcoxon rank-sum test and two-sample tests of proportions as appropriate. Differences between subgroups in levels of either IL-6 or TNFα were analyzed using Wilcoxon rank-sum tests. Next,

TABLE 1 | Clinical and demographic features of the complete study population of 61 patients with rheumatoid arthritis and a wish to conceive, and subgroups divided by a time to pregnancy (TTP) shorter or longer than 1 year.

Variable	Study population n = 61	TTP < 1 year n = 42	TTP > 1 year n = 19	*p*
Age in years—mean (SD)	31.1 (3.5)	31.1 (3.5)	31.2 (3.5)	0.913
Duration of disease in years—median (IQR)	6.0 (1.7–10.9)	5.5 (2.0–8.6)	9.0 (1.0–13.2)	0.544
DAS28-CRP—mean (SD)	3.76 (0.97)	3.74 (0.99)	3.80 (0.94)	0.833
ACPA positive—n (%)	31 (51)	19 (45)	12 (63)	0.241
RF positive—n (%)	35 (57)	22 (52)	13 (68)	0.195
Erosive disease—n (%)	34 (56)	22 (52)	12 (63)	0.433
Nulliparity—n (%)	35 (57)	24 (57)	11 (58)	0.956
Medication preconception—n (%)				
None	21 (34)	17 (40)	4 (21)	0.139
NSAIDs	20 (33)	11 (26)	9 (47)	0.103
Prednisone	26 (43)	*14 (33)*	*12 (63)*	*0.029**
Sulfasalazine	19 (31)	15 (36)	4 (21)	0.252
Hydroxychoroquine	2 (3)	1 (2.4)	1 (5.3)	0.558
Gold therapy	2 (3)	2 (4.8)	0 (0)	0.333
Azathioprine	1 (2)	0 (0)	1 (5.3)	0.134
Etanercept	1 (2)	1 (2.4)	0 (0)	0.498

*ACPA, anti-citrullinated peptide antibodies; RF, rheumatoid factor; DAS28-CRP, 28-joint disease Activity Score with three variables based on the C-reactive protein level; NSAIDs, non-steroidal anti-inflammatory drugs. *= $p < 0.05$*

patients were stratified in either high or low IL-6 or TNFα based on the median. Study population characteristic differences between high and low cytokine level subgroups were analyzed using two-sample t tests, Wilcoxon rank-sum test and two-sample tests of proportions as appropriate. Differences in time to pregnancy between high and low level cytokine categories were studied using Kaplan–Meier survival curves. Significance between curves was determined using a Gehan–Breslow–Wilcoxon test. Furthermore, cox regression analyses were performed. First, univariate cox regression analyses for time to pregnancy and IL-6 or TNFα were performed. This was followed by multivariable cox regression analyses with variables DAS28-CRP and IL-6 or TNFα. Next, multivariable cox regression analyses were executed including variables age, disease activity, nulliparity, non-steroidal anti-inflammatory drug (NSAID) use and prednisone use next to IL-6 or TNFα. These variables were chosen in line with literature (Brouwer et al., 2015). Since in literature some reproduction disorders have been shown to be associated with increased IL-6 and TNFα levels, also a subgroup analysis was performed excluding all patients who had been diagnosed with a disorder leading to decreased fertility. In addition, those patients with a partner with a known male cause for subfertility were excluded. As CRP is strongly associated with IL-6 in literature (Tanaka et al., 2014), it was investigated whether for daily clinical practice IL-6 could be replaced by CRP in the analyses. For this purpose, Spearman's correlation of IL-6 and CRP was executed and the same cox regression analyses were performed with CRP levels instead of IL-6 levels to investigate if outcomes are similar. Statistical analyses were two-tailed and results were considered significant if $p < 0.05$. All analyses were performed using Stata 15 (StataCorp LLC).

RESULTS

Study Population

We included 61 out of 373 RA patients with a wish to conceive from the PARA cohort. These patients had IL-6 and TNFα levels determined at their preconception visit as well as clinical data available. For three patients, IL-6 and TNFα levels were measured at the second preconception visit, when they had been actively trying to conceive for 1 year. The mean age (SD) of the study population was 31.1 (3.5) years, duration of disease (IQR) was 6.0 (1.7–10.9) years and mean disease activity (DAS28-CRP) prior to conception (SD) was 3.76 (0.97). Of all included patients, 31 (51%) were anti-citrullinated peptide antibodies (ACPA) positive, 35 (57%) were rheumatoid factor positive, 34 (56%) had erosive disease, 35 (57%) were nulliparous and 19 (31%) had a time to pregnancy >12 months. The following medication was used: sulfasalazine by 19 (31%) patients, hydroxychloroquine by 2 (3%), prednisone by 26 (43%), azathioprine by 1 (2%) patient, etanercept by 1 (2%) patient and gold therapy by 2 (3%) patients. Subgroup analysis showed higher prednisone use in patients with a time to pregnancy longer than 12 months. Described characteristics can be found in **Table 1**.

Fourty six out of all 61 (75.4%) patients responded to the invite for follow-up study for investigation of reproduction and fertility. Of this population, eight patients (17.4%) were diagnosed with a reproductive disorder: four patients out of 46 (8.7%) were diagnosed with anovulation, 1 (2.2%) with endometriosis, 1 (2.2%) with early menopause, 1 (2.2%) with blockage of fallopian tubes, 1 (2.2%) patient with a male factor influencing fertility and 1 (2.2%) patient with anovulation as well as a male factor.

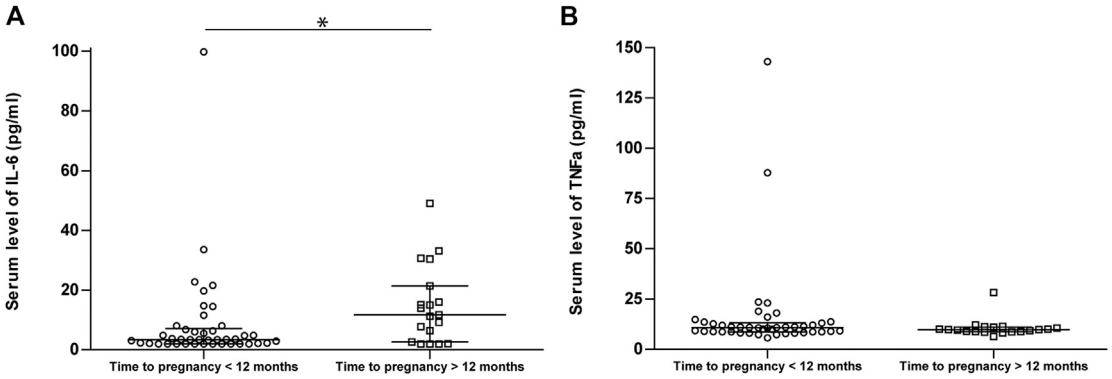


FIGURE 1 | Boxplots showing interleukin 6 (IL-6) and tumor necrosis factor alpha distributions with median and interquartile range stratified by time to pregnancy (**A,B**, respectively). The *y*-axis represents serum cytokine levels of Rheumatoid Arthritis patients with a wish to conceive (pg/ml), the *x*-axis shows patient groups stratified for time to pregnancy. IL-6 levels were statistically significant higher in patients with a time to pregnancy >12 months compared to patients with a time to pregnancy <12 months ($p = 0.016$) **(A)**. * = $p < 0.05$.

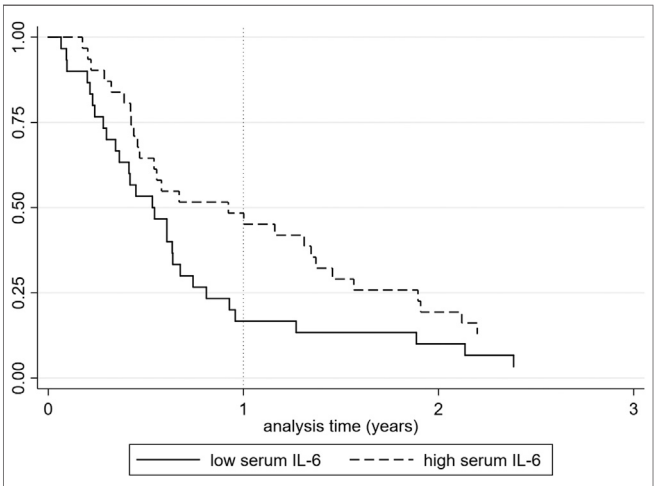


FIGURE 2 | Kaplan-Meier survival curves showing time to pregnancy in interleukin 6 (IL-6) high ($n = 31$) vs. IL-6 low (n = 30) patients. The *y*-axis shows the proportion of patients who are not yet pregnant, the *x*-axis shows the analysis time (years). The survival curve shows that time to pregnancy is longer for patients with high levels of IL-6 ($p = 0.045$).

Serum Interleukin 6 and Tumor Necrosis Factor Alpha Levels

In 14 out of 61 (23.0%) observations, IL-6 measurements were below the detection limit. Therefore, for all measurements below the detection limit, the IL-6 level was defined at the threshold value of 2.0 pg/ml. IL-6 medians (IQR) were 3.44 (2.0–6.77) and 11.7 (2.67–21.4) pg/ml for patients with a time to pregnancy <12 months ($n = 42$) and patients with a time to pregnancy >12 months ($n = 19$), respectively. IL-6 levels were significantly higher in patients with a time to pregnancy longer than 1 year ($p = 0.016$).

For TNFα, all measurements were above the detection limit. TNFα median serum levels (IQR) were 9.76 (8.78–11.1) pg/ml for patients with a time to pregnancy <12 months and 10.75 (8.72–13.0) pg/ml for patients with a time to pregnancy >12 months. There was no significant difference between these groups ($p = 0.33$). Boxplots depicting IL-6 and TNFα distributions categorized by time to pregnancy are shown in **Figures 1A,B**, respectively.

Interleukin 6 and Time to Pregnancy

Patients were stratified in IL-6 low and IL-6 high categories based on the median IL-6 level of the complete study population (median = 4.75 pg/ml). In the IL-6 high subgroup, disease activity (DAS28-CRP) was higher, patients used more NSAIDs and medication use in general was more frequent than in the IL-6 low group ($p = 0.0005$, $p = 0.0364$ and $p = 0.0022$, respectively). Kaplan–Meier survival analysis ($n = 61$) shows a different time to pregnancy between the groups with either high or low IL-6. The group with high IL-6 shows a prolonged time to pregnancy compared to the group with low levels of serum IL-6 ($p = 0.045$). This survival curve is shown in **Figure 2**.

IL-6 levels were logarithmically transformed before being imputed in the regression analysis. Univariate cox regression analysis showed that IL-6 is associated with time to pregnancy: hazard ratio (HR) 0.68 (95% CI: 0.51–0.93, $p = 0.015$). Cox regression analysis with the variables IL-6 and DAS28-CRP showed that higher IL-6 scores were associated with a reduced chance of pregnancy, corrected for disease activity: HR for IL-6 0.66 (95% CI: 0.46–0.94, $p = 0.022$). The multivariate cox regression, with variables IL-6, age, disease activity, nulliparity, NSAID use and prednisone use showed a significant association between IL-6 and time to pregnancy with a HR 0.66 (95% CI: 0.43–0.99, $p = 0.044$).

Furthermore, using the data from the follow-up study ($n = 46$), all patients with a diagnosis of a reproductive disorder that could explain decreased fertility ($n = 8$) were excluded in a subgroup analysis. Seven out of eight exclusions belonged to the subfertile group with a time to pregnancy longer than 12 months. Their median (IQR) IL-6 level was 7.86 (1.34–27.35) pg/ml. Univariate analysis of IL-6 ($n = 38$) showed a significant association of IL-6 levels with time to

pregnancy: HR 0.69 (95% CI: 0.48–0.99, p = 0.046). Next, multivariate analysis with variables IL-6, age, disease activity, nulliparity, NSAID use and prednisone in relation to time to pregnancy was performed on the same subgroup (n = 38) and showed a significant association between IL-6 and time to pregnancy: HR 0.54 (95% CI: 0.32–0.92, p = 0.023).

Tumor Necrosis Factor Alpha and Time to Pregnancy

After stratification of patients in TNFα low and high categories by the median of 9.76 pg/ml, patients in the TNFα high subgroup had longer duration of disease (p = 0.0182). Survival analysis for TNFα stratified by high and low serum levels did not show the same pattern as IL-6. Kaplan Meier survival (n = 61) showed that having high or low serum TNFα did not have an effect on time to pregnancy (p = 0.62). Levels of TNFα were logarithmically transformed before being imputed into the models. Univariate cox regression analysis showed that TNFα is not associated with time to pregnancy: HR 1.41 (95% CI: 0.88–2.24, p = 0.15). Cox regression analysis with the variables TNFα and DAS28-CRP and analysis with variables TNFα, age, disease activity, nulliparity, NSAID use and prednisone use did not show an effect of TNFα on the probability of pregnancy: HR 1.41 (95% CI: 0.90–2.25, p = 0.14) and HR 1.34 (95% CI: 0.75–2.39, p = 0.33), respectively. Univariate analysis of the subgroup excluding all patients with a reproductive disorder or a male factor [median (IQR) TNFα level of excluded patients: 8.62 (8.10–9.29) pg/ml] that could explain decreased fertility (n = 38) showed no association of TNFα with time to pregnancy: HR 1.12 (95% CI: 0.63–1.98, p = 0.69). Lastly, multivariate analysis on the same subgroup including TNFα, age, disease activity, nulliparity, NSAID use and prednisone in relation to time to pregnancy did not show an association between TNFα levels and time to pregnancy: HR 1.41 (95% CI: 0.71–2.78, p = 0.31).

C-Reactive Protein and Time to Pregnancy

IL-6 and CRP levels are strongly correlated in our study population (Spearman's rank correlation, r_s = 0.71). CRP values were log transformed for cox regression analyses. Univariate analysis of CRP in relation to time to pregnancy showed a significant effect on time to pregnancy: HR 0.81 (95% CI: 0.65–1.00, p = 0.048). Multivariate cox regression analysis with the variables CRP and DAS28-CRP and analysis with variables CRP, age, disease activity, nulliparity, NSAID use and prednisone use both showed an association between CRP levels and time to pregnancy: HR 0.76 (95% CI: 0.59–0.99, p = 0.044) and HR 0.76 (95% CI: 0.59–0.98, p = 0.036), respectively. No significant association between CRP and time to pregnancy was found in the subgroup analyses excluding patients with a reproductive disorder or a male factor that could explain decreased fertility (n = 38) (univariate analysis HR 0.83 (95% CI: 0.64–1.06, p = 0.137); multivariate analysis with variables CRP, age, disease activity, nulliparity, NSAID use and prednisone use HR 0.74 (95% CI: 0.53–1.03, p = 0.075).

DISCUSSION

Our study is the first to evaluate IL-6 and TNFα as potential influencing factors of subfertility in RA patients. We showed that IL-6 is increased in RA patients with a time to pregnancy longer than 12 months. High IL-6 levels are associated with a prolonged time to pregnancy, even when corrected for potential confounders, like disease activity, medication and diagnosis of reproductive disorders, in a large cohort of RA patients with a wish to conceive. For TNFα levels, no association with fertility was found.

This report, combined with previous studies on the link between IL-6 and reproductive disorders and fertility (Demir et al., 2009; Peng et al., 2016; Wang F. et al., 2018; Wang X. M. et al., 2018), provides an indication that high levels of circulating IL-6 hamper fertility. However, the biological mechanisms behind this phenomenon are not known. A possible explanation could be the role of IL-6 in T cell differentiation. IL-6 is a known influencer thereof, driving follicular helper T cell differentiation and enabling T helper 17 cell over regulatory T cell differentiation (Schinnerling et al., 2017). A disturbed T helper 17 and regulatory T cell balance has been associated with fertility and pregnancy disorders through lack of immunologic tolerance, which is pivotal for implantation and pregnancy maintenance (Jasper et al., 2006; Figueiredo and Schumacher, 2016).

Despite the association between IL-6 and fertility, IL-6 might not directly be involved in subfertility pathogenesis. It is possible IL-6 is a proxy for something else, such as a disease related factor. For example, IL-6 levels are known to be associated with disease activity (Madhok et al., 1993). Therefore, in our analyses, a correction was made for disease activity score and other possible confounders based on literature. Another possibility is that IL-6 could be a proxy for other factors in the same inflammatory cascade. Fertility immunology is an upcoming field and exact mechanisms surrounding conception and implantation, certainly within RA patients, are yet to be resolved. More research on fertility biology is needed to elucidate the exact role of IL-6 as well as T helper subset balance in this matter.

Within the subgroup with a time to pregnancy shorter than 1 year, some patients with high IL-6 levels are present (**Figure 1A**). However, since there is only one cytokine measurement available representing the complete preconception time period, it is unclear if cytokines levels were stable in these patients. A possible explanation for these outliers, next to chance, is temporarily high IL-6 levels in the context of infection.

Since decreased fertility is an important issue in women with RA during reproductive age, treatment of patients with a wish to conceive should not only target the immune system in a way that controls maternal disease activity, but also take into account how therapy could affect fertility. Based on this study, the IL-6 pathway might be considered as a therapeutic target in patients with RA and a wish to conceive. Therapies directed at the IL-6 receptor, such as tocilizumab, could be a promising option for those patients. However, for these therapeutic agents, little is known about drug safety during pregnancy. Due to lack of

safety data, current guidelines state that tocilizumab should be stopped in RA patients with a wish to conceive (Götestam Skorpen et al., 2016). Small studies report no adverse pregnancy outcomes in patients exposed to tocilizumab, but numbers are too limited to be conclusive on the matter (Nakajima et al., 2016). Consequently, to this date, tocilizumab is not an appropriate therapeutic option for RA patients in the time period before pregnancy, but could be seriously considered in the future, when there is more clarity on teratogenicity.

Meanwhile, TNFα inhibition (TNFi) is a widely used treatment option for RA and current guidelines state that TNFα inhibitors are appropriate therapeutic agents for patients with a wish to conceive (Götestam Skorpen et al., 2016; Sammaritano et al., 2020). Although our analyses show no correlation of circulating TNFα-levels with fertility, TNFα is a driver of IL-6 and use of TNFi has been shown to decrease circulating IL-6 levels (Charles et al., 1999). Moreover, TNFi has been reported to expand regulatory T cells (Nguyen and Ehrenstein, 2016). Therefore, treatment with TNFi could be a potential option to increase fertility in women with active RA. In a small study, it was indeed reported that TNFi decreases time to pregnancy in RA patients with a wish to conceive (Shimada et al., 2019). Potential effects of TNFi on pregnancy outcomes should be considered. Increased risks associated with TNFi of preterm birth, caesarean section and small for gestational age children have been previously reported (Bröms et al., 2020). However, given the study design and the fact that high disease activity is known to negatively influence pregnancy outcomes (Smeele and Dolhain, 2019), these effects might not be drug-derived, but due to confounding by indication.

Given the fact that IL-6 serum levels are correlated to disease activity (Madhok et al., 1993), as also displayed by our results, effective treatment of RA patients with other DMARDs such as sulfasalazine presumably decrease IL-6 levels and possibly enhance fertility as well. More evidence on the effect of different DMARDs on fertility from large cohort studies is needed to confirm this effect and to further elucidate the mechanisms behind it.

In daily clinical practice, IL-6 levels are not routinely measured. This makes the possibility to use IL-6 levels as a potential biomarker for fertility in RA patients with a wish to conceive less practical. However, IL-6 is a strong driver of CRP and high CRP levels are predictive for high IL-6 (Tanaka et al., 2014). For that reason all analyses were performed with CRP instead of IL-6 and for the main analyses similar results were found. Therefore, in daily practice, when no IL-6 levels are available, also CRP is a potential indicator for time to pregnancy in RA-patients with a wish to conceive. Analysis of a larger patient population would give more insight into the value of CRP as a clinical biomarker for fertility.

No association of TNFα levels with fertility was found. This raises the question whether our study is adequately powered to show the potential influence of TNFα on fertility. A post-hoc power calculation shows that, based on the data in this study, over 1,300 patient inclusions are needed to demonstrate a statistically significant difference. This is an indication that a potential difference in TNFα levels is probably not clinically relevant.

Previous reports have shown the PARA cohort to be a representative study population. However, cytokine levels were only determined in samples of patients who had serum from the preconception time point available and who had eventually successfully achieved pregnancy and delivered a child, because of previous research purposes (de Steenwinkel et al., 2013). This led to inclusion of 61 out of 373 total patients in the PARA cohort. Nevertheless, we do not expect that this causes the results to be invalid. Our study population is skewed to a relatively more fertile subgroup of the complete PARA cohort and the results still show an association between IL-6 and time to pregnancy. Although it is presumable that IL-6 levels are high in infertile RA patients as well, this group is not represented in the study population and should be further investigated.

In conclusion, this study shows that high IL-6 levels, but not TNFα, are associated with decreased fertility in women with RA and a wish to conceive. This finding provides a rationale to therapeutically target the IL-6 pathway in the time period before pregnancy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Erasmus MC medical ethics review board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MB and HS drafted the work, analyzed the data and wrote the manuscript. EL and RD critically revised the text and figures. All authors approved the final manuscript for publication.

FUNDING

This work was supported by the Dutch Arthritis Foundation (ReumaNederland) (project numbers: LLP-26 and NR 19-2-401) and UCB Pharma. The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication.

ACKNOWLEDGMENTS

The authors are grateful to all patients who participated in the PARA study. Additionally, they thank Yaël de Man, Fleur van de Geijn, Esther Gasthuis, Florentien de Steenwinkel, Jenny Brouwer and all laboratory workers and research assistants for their contribution to the data collection.

REFERENCES

Arnett, F. C., Edworthy, S. M., Bloch, D. A., McShane, D. J., Fries, J. F., Cooper, N. S., et al. (1988). The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 31 (3), 315–324. doi:10.1002/art.1780310302

Bröms, G., Kieler, H., Ekbom, A., Gissler, M., Hellgren, K., Lahesmaa-Korpinen, A. M., et al. (2020). Anti-TNF treatment during pregnancy and birth outcomes: a population-based study from Denmark, Finland, and Sweden. *Pharmacoepidemiol. Drug Saf.* 29 (3), 316–327. doi:10.1002/pds.4930

Brouwer, J., Hazes, J. M., Laven, J. S., and Dolhain, R. J. (2015). Fertility in women with rheumatoid arthritis: influence of disease activity and medication. *Ann. Rheum. Dis.* 74 (10), 1836–1841. doi:10.1136/annrheumdis-2014-205383

Charles, P., Elliott, M. J., Davis, D., Potter, A., Kalden, J. R., Antoni, C., et al. (1999). Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. *J. Immunol.* 163 (3), 1521–1528.

de Man, Y. A., Dolhain, R. J., van de Geijn, F. E., Willemsen, S. P., and Hazes, J. M. (2008). Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum.* 59 (9), 1241–1248. doi:10.1002/art.24003

de Steenwinkel, F. D., Hokken-Koelega, A. C., de Man, Y. A., de Rijke, Y. B., de Ridder, M. A., Hazes, J. M., et al. (2013). Circulating maternal cytokines influence fetal growth in pregnant women with rheumatoid arthritis. *Ann. Rheum. Dis.* 72 (12), 1995–2001. doi:10.1136/annrheumdis-2012-202539

Demir, B., Guven, S., Guven, E. S., Atamer, Y., and Gul, T. (2009). Serum IL-6 level may have role in the pathophysiology of unexplained infertility. *Am. J. Reprod. Immunol.* 62 (4), 261–267. doi:10.1111/j.1600-0897.2009.00734.x

Ebejer, K., and Calleja-Agius, J. (2013). The role of cytokines in polycystic ovarian syndrome. *Gynecol. Endocrinol.* 29 (6), 536–540. doi:10.3109/09513590.2012.760195

Figueiredo, A. S., and Schumacher, A. (2016). The T helper type 17/regulatory T cell paradigm in pregnancy. *Immunology* 148 (1), 13–21. doi:10.1111/imm.12595

Fransen, J., and van Riel, P. L. (2009). The disease activity score and the EULAR response criteria. *Rheum. Dis. Clin. N. Am.* 35 (4), 745–viii. doi:10.1016/j.rdc.2009.10.001

Götestam Skorpen, C., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., et al. (2016). The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheum. Dis.* 75 (5), 795–810. doi:10.1136/annrheumdis-2015-208840

Iwabe, T., Harada, T., and Terakawa, N. (2002). Role of cytokines in endometriosis-associated infertility. *Gynecol. Obstet. Invest.* 53 (Suppl. 1), 19–25.

Jasper, M. J., Tremellen, K. P., and Robertson, S. A. (2006). Primary unexplained infertility is associated with reduced expression of the T-regulatory cell transcription factor Foxp3 in endometrial tissue. *Mol. Hum. Reprod.* 12 (5), 301–308. doi:10.1093/molehr/gal032

Kang, S., Tanaka, T., Narazaki, M., and Kishimoto, T. (2019). Targeting interleukin-6 signaling in clinic. *Immunity* 50 (4), 1007–1023. doi:10.1016/j.immuni.2019.03.026

Madhok, R., Crilly, A., Watson, J., and Capell, H. A. (1993). Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. *Ann. Rheum. Dis.* 52 (3), 232–234. doi:10.1136/ard.52.3.232

Markert, U. R., Morales-Prieto, D. M., and Fitzgerald, J. S. (2011). Understanding the link between the IL-6 cytokine family and pregnancy: implications for future therapeutics. *Expet Rev. Clin. Immunol.* 7 (5), 603–609. doi:10.1586/eci.11.60

McInnes, I. B., and Schett, G. (2017). Pathogenetic insights from the treatment of rheumatoid arthritis. *Lancet* 389 (10086), 2328–2337. doi:10.1016/S0140-6736(17)31472-1

Nakajima, K., Watanabe, O., Mochizuki, M., Nakasone, A., Ishizuka, N., and Murashima, A. (2016). Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. *Mod. Rheumatol.* 26 (5), 667–671. doi:10.3109/14397595.2016.1147405

Nguyen, D. X., and Ehrenstein, M. R. (2016). Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF-TNF-RII binding in rheumatoid arthritis. *J. Exp. Med.* 213 (7), 1241–1253. doi:10.1084/jem.20151255

Peng, Z., Sun, Y., Lv, X., Zhang, H., Liu, C., and Dai, S. (2016). Interleukin-6 levels in women with polycystic ovary syndrome: a systematic review and meta-analysis. *PLoS One* 11 (2), e0148531. doi:10.1371/journal.pone.0148531

Sammaritano, L. R., Bermas, B. L., Chakravarty, E. E., Chambers, C., Clowse, M. E. B., Lockshin, M. D., et al. (2020). American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol.* 72 (4), 529–556.

Schinnerling, K., Aguillón, J. C., Catalán, D., and Soto, L. (2017). The role of interleukin-6 signalling and its therapeutic blockage in skewing the T cell balance in rheumatoid arthritis. *Clin. Exp. Immunol.* 189 (1), 12–20. doi:10.1111/cei.12966

Shimada, H., Kameda, T., Kanenishi, K., Miyatake, N., Nakashima, S., Wakiya, R., et al. (2019). Effect of biologic disease-modifying anti-rheumatic drugs for patients with rheumatoid arthritis who hope to become mothers. *Clin. Rheumatol.* 38 (5), 1453–1458. doi:10.1007/s10067-019-04450-3

Smeele, H. T. W., and Dolhain, R. J. E. M. (2019). Current perspectives on fertility, pregnancy and childbirth in patients with rheumatoid arthritis. *Semin. Arthritis Rheum.* 49 (3S), S32–S5. doi:10.1016/j.semarthrit.2019.09.010

Smolen, J. S., Aletaha, D., and McInnes, I. B. (2016). Rheumatoid arthritis. *Lancet* 388 (10055), 2023–2038. doi:10.1016/S0140-6736(16)30173-8

Tanaka, T., Narazaki, M., and Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. *Cold Spring Harb. Perspect. Biol.* 6 (10), a016295. doi:10.1101/cshperspect.a016295

Taylor, P. C., and Feldmann, M. (2009). Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. *Nat. Rev. Rheumatol.* 5 (10), 578–582. doi:10.1038/nrrheum.2009.181

Wang, F., Wang, H., Jin, D., and Zhang, Y. (2018). Serum miR-17, IL-4, and IL-6 levels for diagnosis of endometriosis. *Medicine* 97 (24), e10853. doi:10.1097/MD.0000000000010853

Wang, X. M., Ma, Z. Y., and Song, N. (2018). Inflammatory cytokines IL-6, IL-10, IL-13, TNF-α and peritoneal fluid flora were associated with infertility in patients with endometriosis. *Eur. Rev. Med. Pharmacol. Sci.* 22 (9), 2513–2518. doi:10.26355/eurrev_201805_14899

Wu, M. Y., and Ho, H. N. (2003). The role of cytokines in endometriosis. *Am. J. Reprod. Immunol.* 49 (5), 285–296. doi:10.1034/j.1600-0897.2003.01207.x

Yoshida, Y., and Tanaka, T. (2014). Interleukin 6 and rheumatoid arthritis. *BioMed. Res. Int.* 2014, 698313. doi:10.1155/2014/698313

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 16 December 2020
doi: 10.3389/fphar.2020.613239

Neuropsychiatric Outcome of Children Born to Women With Systemic Lupus Erythematosus and Exposed *in Utero* to Azathioprine: A Case-Control Study

Maria-Grazia Lazzaroni[1,2*†], *Laura Andreoli*[1,2†], *Francesca Crisafulli*[1,2], *Francesco Tamborini*[3], *Irene Debeni*[1], *Valentina Binda*[3], *Cecilia Nalli*[2], *Jessica Galli*[1,4], *Elisa Fazzi*[1,4], *Gabriella Moroni*[3], *Franco Franceschini*[1,2] *and Angela Tincani*[1,2,5]

[1]*Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy,* [2]*Rheumatology and Clinical Immunology Unit, ASST Spedali Civili of Brescia, Brescia, Italy,* [3]*Nephrology Unit, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy,* [4]*Neuropsychiatry Unit, Children's Hospital, ASST Spedali Civili of Brescia, Brescia, Italy,* [5]*I.M. Sechenov First Moscow State Medical University, Moscow, Russia*

OPEN ACCESS

Edited by:
Cecilia Beatrice Chighizola, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Marianne Wallenius, Norwegian University of Science and Technology, Norway
Arsene Mekinian, Assistance Publique Hôpitaux de Paris (APHP), France

***Correspondence:**
Maria-Grazia Lazzaroni
mariagrazialazzaroni@gmail.com

†These authors have contributed equally to this work.

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *01 October 2020*
Accepted: *19 November 2020*
Published: *16 December 2020*

Citation:
Lazzaroni M-G, Andreoli L, Crisafulli F, Tamborini F, Debeni I, Binda V, Nalli C, Galli J, Fazzi E, Moroni G, Franceschini F and Tincani A (2020) Neuropsychiatric Outcome of Children Born to Women With Systemic Lupus Erythematosus and Exposed in Utero *to Azathioprine: A Case-Control Study. Front. Pharmacol. 11:613239. doi: 10.3389/fphar.2020.613239*

Objective: The long-term outcome of children born to SLE mothers still represents a controversial topic in literature, with some studies reporting a possible increased prevalence of different neurologic and psychiatric diseases (NPD), including neurodevelopmental disorders (ND), and in particular learning disorders (LD). Different risk factors have been advocated, such as the *in utero* exposure to auto-antibodies and drugs, particularly Azathioprine (AZA).

Methods: A case-control study was designed to compare pregnancies treated with AZA (cases) with those not treated with AZA (controls). All the pregnancies had been prospectively followed in two Italian centers. The match was based upon renal involvement, antiphospholipid (aPL) status, maternal age at pregnancy (±5 years) and child's age at the time of the study (±2 years). SLE mothers were interviewed by a telephone survey, particularly focused on the presence of a certified NPD in their children ≥6 years of age.

Results: Twenty-seven cases and 65 controls were similar in terms of demographic, immunological and clinical features, except for a higher rate of SLE flares during pregnancy in cases (22.2% vs. 10.8%, *p*:0.191). The 92 children had a mean age of 14.0 years at the time of the survey; 11 had at least one NPD (12.0%). The frequency of each single NPD was similar to that of the general pediatric population and no association was found with either the *in utero* exposure to AZA, or other specific factors (auto-antibodies, disease activity, obstetric complications, prematurity).

Conclusion: The long-term neuropsychiatric outcome of the children born to SLE mothers did not show neither an increased frequency of NPD as compared to the general pediatric population nor a specific pattern of NPD. The *in utero* exposure to AZA was not associated with the development of NPD in this case-control study of prospectively-followed pregnancies. NPD are complex conditions and large prospective studies are needed to capture the wide range of variables that may contribute to their development in the offspring of SLE women.

Keywords: azathioprine, offspring, neurodevelopmental disorders, learning disabilities, pregnancy, systemic lupus erythematosus

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease mostly affecting women of childbearing age (Gergianaki et al., 2018). In the last decades, the rate of successful pregnancies for these women has greatly increased, thanks to the general improvement in SLE management, but also to the availability of drugs compatible with pregnancy and lactation (Lazzaroni et al., 2016). Pregnancy in SLE requires a multidisciplinary approach, with an accurate preconception counseling and a close monitoring, helping to reduce maternal flares and obstetric and neonatal complications (Andreoli et al., 2017). Besides the impact of the disease on pregnancy outcome, another topic is of utmost interest for patients who wish to become mothers: the short- and the long-term outcome of their children.

A recent large multicentre Italian survey, focused on the impact of SLE and other rheumatic diseases on family planning, revealed that most of these women were concerned about the impact of their disease on parenting capacity, but also the possible harmful effects of drugs assumed during pregnancy and lactation on the growth of their offspring (Andreoli et al., 2019). These concerns were often the reason why these women had fewer children than desired. The same study also revealed that patients had poor knowledge about reproductive issues, mainly because of the lack of discussion with health care providers.

Altogether, these data highlight the urgent need of an informative and exhaustive preconception counseling and a close monitoring during pregnancy by a multidisciplinary team, also encompassing the topic of "children's health".

Reassuring data about the short-term outcome of these children, in terms of neonatal complications and possible teratogenic effects of the drugs, have become available in the past few years. It is now needed to clarify the long-term outcome of the offspring of SLE mothers (Yengej et al., 2017). In fact, some studies raised the possibility of an increased frequency of different neuro-psychiatric disorders (NPD), including neurodevelopmental disorders (ND), such as learning disabilities (LD) and autism spectrum disorders (ASD), even if a normal intelligence level was reported (Urowitz et al., 2008; Nalli et al., 2020). Specifically, two case-control studies highlighted an increased frequency of LD in the offspring of SLE patients, particularly regarding male children (McAllister et al., 1997; Ross et al., 2003). More recently, a large population study based on the OSLER registry (Offspring of SLE Mothers Registry) found an increased risk of ASD, even though the overall prevalence was very low in absolute terms (Vinet et al., 2015).

In order to explain this increased frequency of NPD, different potential risk factors have been advocated. Apart from general social and familiar risk factors, such as coping with a mother affected by a chronic disease, specific SLE-related factors have been considered. In particular, the transplacental passage of maternal autoantibodies and/or drugs could be responsible for NPD by crossing the incomplete blood-brain barrier and binding to neuronal cells in the developing central nervous system of the fetus (Nalli et al., 2020).

The presence of anti-Ro/SSA antibodies was reported to be associated with an increased risk of LD in children of SLE patients (Ross et al., 2003; Urowitz et al., 2008). However, a study evaluating the neurodevelopmental outcome in 13 children born with congenital heart block, a disease which is strongly associated with these antibodies, found a normal intelligence quotient and only one case of a mild LD (Brucato et al., 2006). Antiphospholipid antibodies (aPL) have been associated with NPD (Motta et al., 2006), including ND and behavioral disorders, but also with increased usage of special educational services (Abisror et al., 2013; Mekinian et al., 2013; Marder et al., 2014).

Regarding the potential role of drugs commonly prescribed in SLE pregnancies, special attention was raised on Azathioprine (AZA) and its metabolites (Belizna et al., 2020). AZA is an immunosuppressive drug widely used in SLE patients, especially to maintain remission, and is considered safe during pregnancy as supported by international guidelines (Skorpen et al., 2016; Andreoli et al., 2017).

As maternal treatment is crucial for keeping the disease under control and favoring a good pregnancy outcome, it is important to achieve the patient's compliance by providing reassuring data about the use of drugs during pregnancy. Therefore, we designed a case-control study to elucidate the effects of *in utero* exposure to AZA in children born to women with SLE.

MATERIALS AND METHODS

Study Design

The present study was designed as a retrospective case-control study including pregnancies of SLE patients prospectively followed in two Italian centers (Brescia, Milano). SLE pregnancies treated with AZA formed the group of cases, while SLE pregnancies not treated with AZA formed the control group. The match between one case with two or, if possible three controls, was based on the subsequent characteristics: renal involvement (present/absent); aPL status at the beginning of pregnancy (positive/negative); age of the mother at the beginning of pregnancy (±5 years); age of the child at the time of the study (±2 years).

The study was performed according to the principles of the Declaration of Helsinki and was approved by all the Local Ethic Committees (approval number 2917 in the Promoting Center). All patients signed a written informed consent.

Inclusion and Exclusion Criteria

Women with SLE diagnosis fulfilling the 1997 ACR classification criteria (Hochberg, 1997) were considered if they had a singleton pregnancy yielding a live birth. Only children of school age (≥6 years) at the time of interview were included in the study.

Twin Pregnancies and pregnancy losses defined as spontaneous abortion (<10th gestational weeks) or intrauterine fetal death (≥10th gestational weeks) were excluded.

Clinical and Immunological Features of Mothers and Children

Data regarding clinical and laboratory features were retrospectively retrieved from medical charts from the two centers and collected in a common database.

The following maternal features were collected: age at disease onset, age at the beginning of pregnancy; disease duration at the beginning of pregnancy; presence of SLE renal involvement; occurrence and type of disease flare during pregnancy; therapy prescribed during pregnancy, including Hydroxychloroquine (HCQ), AZA, Cyclosporine or other immunosuppressants, corticosteroids as mean weekly dosage of prednisone equivalent; occurrence of pregnancy complications.

Neonatal Features Collected Were Gestational Week at Birth, Birth Weight and Sex

The immunological tests were performed during pregnancy in each of the two participating centers, by certified laboratories fulfilling European quality standards. Antinuclear antibodies (ANA), antibodies to extractable nuclear antigens (anti-ENA) and aPL were detected as for clinical practice. A complete aPL profile composed by the three criteria assays was available for each subject; each assay was considered positive if confirmed at least 12 weeks apart.

Long-Term Neuropsychiatric Outcome of Children

The long-term neuropsychiatric outcome of the children was assessed through a specifically designed telephone interview in a time interval comprised between May 2019 and May 2020. Questions concerned the presence of different neurologic and psychiatric disorders (NPD) and included the subsequent diagnosis:

- Neurodevelopmental Disorders (ND): Attention-Deficit/ Hyperactive Disorder (ADHD), Learning Disabilities (LD) including dyslexia, dysgraphia, dyscalculia, dysorthography, Communication Disorders, Autism Spectrum Disorder (ASD);
- Psychomotor delay;
- Behavioral disorders including aggressiveness, depression/ anxiety, hyperactivity;
- Other neurological disorders: epilepsy; migraine.

Only disorders which had been certified by a child neurologist or psychiatrist were considered. Information regarding the repetition of school years was also collected.

Statistical Analysis

Continuous variables were reported as mean value and standard deviation, whereas categorical variables as proportion and/or percentage. T-student's test for continuous variables and Fisher's exact test or Chi-square test for categorical variables were applied as appropriate. p values < 0.05 were considered significant.

RESULTS

Description of the Cohort

Pregnancies Characteristics

The study included 92 singleton pregnancies resulted in live births of 76 SLE patients from two Italian referral centers (Brescia n = 43, Milano n = 33) in a period comprised between 1987 and 2014. Fourteen patients had two pregnancies and one patient had three pregnancies. Most of the patients was Caucasian (97.4%), while the remaining two patients were Asian (2.6%). Mean age at the onset of SLE was 23.1 ± 6.5 years and mean disease duration at the beginning of pregnancy was 9.2 ± 6.0 years; renal involvement was present in 50/76 (65.8%). An associated antiphospholipid syndrome (APS) was detected in 11/76 (14.5%) patients and autoimmune thyroiditis in 7.9%.

At the beginning of pregnancy, the mean age of the mothers was 32.3 ± 4.9 years. A SLE flare during pregnancy occurred in 13/92 (14.1%): nine of 13 total flares were renal (9.8%), three were cutaneous (3.3%), one neurologic and one articular.

Regarding the immunological profile, anti-ENA antibodies were positive in 54 pregnancies (58.7%) and 27 of them were positive for anti-Ro/SSA antibodies (29.3%). aPL positivity was detected in 26.1% of pregnancies: 6.5% had a triple aPL positivity (LAC plus aCL IgG/IgM plus aB2GPI IgG/IgM), 7.6% had double aPL positivity and 11.9% had a single positivity. Only two patients with two pregnancies each had an aPL profile modification between the first and the second pregnancy: in one patient a double positivity turned into negative, while the other patient who was previously aPL negative displayed a single positivity.

Preterm delivery <37th weeks was recorded in 25/92 pregnancies (27.2%), including six preterm deliveries <34th weeks. Pre-eclampsia occurred in 8/92 (9.7%) of pregnancies, while HELLP in 1/92 (1.1%).

Most of the patients were treated with corticosteroids during pregnancy (78.2%), with a mean weekly prednisone dosage of 31.5 mg, while hydroxychloroquine (HCQ) was prescribed in half of the pregnancies (51.1%).

Children's Characteristics

The mean age of the 92 children was 14.0 ± 6.2 years (range: 6–33 years); 47.8% were males. Mean gestational age at birth was 37.0 ± 2.1 weeks and mean birth weight was 2865.3 ± 540.2 g. Small for Gestational Age (SGA) babies were 7/89 (7.9%).

On the basis of the telephone survey, we were able to identify 11 out of 92 children (12.0%) with at least one diagnosis of NPD, as certified by a specialist. One child had epilepsy, one had psychomotor delay, while the other nine had at least one diagnosis of ND; three children had more than one type of NPD. Overall, 11 different diagnosis of ND were recorded: three communication disorders (expressive language delay, 3.3%), two ADHD (2.2%) and six LD (6.5%). Among LD, the most frequent diagnosis was dyslexia, reported in five children (5.4%), including one child with concomitant dyscalculia, dysgraphia and dysorthography (1.1%). The only LD child without dyslexia had dyscalculia and dysgraphia. No cases of ASD were found.

Two cases of behavioral disorders were collected: 1 case of hyperactivity and 1 case of aggressiveness, together with psychomotor delay. The other two children with multiple NPD had expressive language disorder with dyslexia.

Moreover, we recorded two children with migraine (all the 3 with other concomitant ND or LD).

TABLE 1 | Univariate analysis of the case-control study comparing SLE pregnancies treated with AZA (cases; n patients = 22, n pregnancies = 27) and not treated with AZA (controls, n patients = 56, n pregnancies = 65).

	Pregnancies treated with AZA	Pregnancies not treated with AZA	*p*-value
Patients characteristics			
Age at SLE onset (years), *mean (SD)*	23.7 (6.7)	22.9 (6.4)	0.610
Caucasian ethnicity	21/22 (95.5)	55/56 (98.2)	0.487
Renal involvement	15/22 (68.2)	37/56 (66.1)	1.000
Concomitant autoimmune diseases	11/22 (50.0)	22/56 (39.3)	0.450
Antiphospholipid syndrome	5/22 (22.7)	6/56 (10.7)	0.276
Sjögren's syndrome	1/22 (4.6)	2/56 (3.6)	1.000
Rheumatoid arthritis	0/22 (0.0)	1/56 (1.8)	1.000
Autoimmune thyroiditis	1/22 (4.6)	5/56 (8.9)	0.670
Pregnancies characteristics			
Age at pregnancy (years), mean (SD)	32.7 (5.9)	32.1 (4.4)	0.565
Disease duration at the beginning of pregnancy (years), mean (SD)	9.07 (6.7)	9.20 (5.8)	0.719
Disease flare during pregnancy	6/27 (22.2)	7/65 (10.8)	0.191
Renal	2/27 (7.4)	7/65 (10.8)	1.000
Cutaneous	3/27 (11.1)	0/65 (0.0)	0.023
Neurologic	1/27 (3.7)	0/65 (0.0)	0.294
Articular	1/27 (3.7)	0/65 (0.0)	0.294
Antiphospholipid antibodies positivity	9/27 (40.7)	15/65 (27.7)	0.311
Triple positivity	1/27 (3.7)	5/65 (7.7)	0.667
Double positivity	4/27 (14.8)	3/65 (4.6)	0.188
Single positivity	4/27 (14.8)	7/65 (10.8)	0.725
Anti-ENA positivity	17/27 (63.0)	38/65 (58.5)	0.816
Anti-Ro/SSA positivity	7/27 (25.9)	21/65 (32.3)	0.625
pPROM (<37th weeks)	1/27 (3.7)	5/65 (7.7)	0.667
HELLP syndrome	0/27 (0.0)	1/65 (1.5)	1.000
Preeclampsia	2/27 (7.4)	6/65 (9.2)	1.000
Treatment during pregnancy			
Corticosteroids	26/27 (96.3)	47/65 (72.3)	0.010
Weekly dose of steroids in prednisone equivalent	39.7 (37.3)	26.9 (27.2)	0.128
Hydroxychloroquine	14/27 (51.9)	33/65 (50.8)	1.000
Cyclosporine-A	0/27 (0.0)	9/65 (13.9)	0.054

HELLP, hemolysis, elevated liver enzymes, and low platelets; pPROM, preterm premature rupture of membranes. Two patients had two pregnancies each, one treated with AZA and one not treated with AZA; therefore, the apparent total number of patients is 78. Results are presented as n/n available data (%), except otherwise indicated.

Case-Control Study

A univariate analysis was performed to compare 27 pregnancies of 22 patients treated with AZA (cases) with 65 matched pregnancies of 56 patients not treated with AZA during pregnancy (controls) (**Table 1**). Two patients had two pregnancies each, one treated with AZA and one not treated with AZA; therefore, the apparent total number of patients is 78.

The two groups did not differ in terms of frequency of renal involvement, aPL positivity, maternal age at the beginning of pregnancy and children age at the time of the interview. These were the characteristics *a priori* selected for matching the two groups. The distribution of aPL profiles (single, double, triple aPL profile according to the number of positive tests) was also homogenous in the two groups. Other clinical and laboratory features were also similar between cases and controls: age at SLE onset and disease duration at the beginning of pregnancy, prevalence of Caucasian ethnicity and other concomitant autoimmune disorders (especially autoimmune thyroiditis) and rate of anti-Ro/SSA positivity.

The frequency of disease flare was higher in cases than in controls, although not statistically significant (22.2% vs. 10.8%, *p*: 0.191); flares were mostly renal in both groups (7.4% vs. 10.8%; *p*: 1.000). Three cutaneous, one neurologic and one articular flare were also observed in the AZA group, while none in the control group.

Regarding therapy during pregnancy, corticosteroids use was more frequent in the AZA group (96.3% vs. 72.3% *p*: 0.010), with a higher mean weekly prednisone-equivalent dosage as compared to controls, although not statistically significant (39.7 ± 37.3 vs. 26.9 ± 27.2 mg, *p*: 0.128). Hydroxychloroquine was prescribed to half of the patients during pregnancy in both groups (51.9% vs. 50.8%; *p*: 1.000).

Among pregnancies not treated with AZA, 9 (13.9%) were treated with Cyclosporine (including 3 with concomitant HCQ), while 30 only with HCQ (46.2%) and 15 only with corticosteroids (23.1%). Eleven patients (16.9%) were not taking any immunosuppressive drugs or corticosteroids during pregnancy.

Considering the 92 children born to the above described 92 pregnancies from 76 SLE mothers (**Table 2**), the mean age at the time of the interview was 12.3 ± 4.9 years in cases and 14.7 ± 6.6 in controls (*p*: 0.165). Male/female ratio, birth weight and gestational age at birth were also similar in the two groups, as well as the rate of prematurity (<37th weeks) or severe prematurity (<34th weeks).

There was no difference in terms of prevalence of NPD, both considering the global prevalence of all the diseases and the single

TABLE 2 | Univariate analysis of the case-control study comparing the outcome of children born to SLE pregnancies included in the study and exposed *in utero* to AZA (n children = 27) vs. not-exposed *in utero* to AZA (n children = 65).

	Children exposed to AZA *in utero*	Children not exposed to AZA *in utero*	*p*-value
Age at the time of the interview, mean (SD)	12.3 (4.9)	14.7 (6.6)	0.165
Male sex	14/27 (51.9)	30/65 (46.2)	0.653
Birth weight (g), mean (SD)	2798.0 (550.2)	2891.6 (538.4)	0.304
Gestational age at birth, mean (SD)	36.8 (2.5)	37.1 (2.0)	0.904
Small for gestational age	0/25 (0.0)	7/64 (10.9)	0.101
Preterm birth (<37th weeks)	8/27 (29.6)	17/65 (26.2)	0.799
Severe preterm birth (<34th weeks)	3/27 (11.1)	3/65 (4.6)	0.354
At least one NPD	3/27 (11.1)	8/65 (12.3)	1.000
ND	2/27 (7.4)	12/65 (18.5)	0.219
ADHD	1/27 (3.7)	1/65 (1.5)	0.503
Communication disorders	1/27 (3.7)	2/65 (3.1)	1.000
Learning disabilities	0/27 (0.0)	6/65 (9.2)	0.175
Dyslexia	0/27 (0.0)	5/65 (7.7)	0.317
Dyscalculia	0/27 (0.0)	2/65 (3.1)	1.000
Dysgraphia	0/27 (0.0)	2/65 (3.1)	1.000
Dysorthography	0/27 (0.0)	1/65 (1.5)	1.000
Behavioral disorders	1/27 (3.7)	1/65 (1.5)	0.502
Psychomotor delay	0/27 (0.0)	1/65 (1.5)	1.000
Epilepsy	1/27 (3.7)	0/65 (0.0)	0.294
Migraine	0/27 (0.0)	2/65 (3.1)	1.000
Repetition of school years	1/27 (3.7)	4/65 (6.2)	1.000

LD, Learning Disabilities; ND, Neurodevelopmental Disorders; NPD, Neuro-Psychiatric Disorders. Results are presented as n/n available data (%), except otherwise indicated.

diagnosis. The frequency of ND, in particular LD, and the repetition of school years, was lower in children exposed *in utero* to AZA, although without a statistically significant difference.

Comparison of Children With and Without Neurodevelopmental Disorders/Learning Disorders

An additional univariate analysis was performed to compare children with at least one diagnosis of NPD (n = 11) and children without any diagnosis of NPD (n = 81) (**Table 3**), in order to identify possible factors associated with these disorders.

The two groups did not significantly differ in terms of maternal disease characteristics or pregnancy features, including specific drugs or maternal autoantibodies exposure during pregnancy. The neonatal features were also similar in the two groups, including weight and gestational age at birth.

DISCUSSION

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disorder, more frequently affecting women in their childbearing age and consequently having a significant impact on family planning and reproductive aspects (Gergianaki et al., 2018). The modifications of their health status determined by pregnancy, the increased risk of obstetric complications, as well as the children outcome are topic of crucial interest for these patients (Andreoli et al., 2017).

The long-term outcome of children born to SLE mothers still represents a controversial topic in literature, with some studies reporting a possible increased prevalence of different neurologic and psychiatric diseases (NPD), including neurodevelopmental disorders (ND), and in particular learning disorders (LD) (Yengej et al., 2017; Nalli et al., 2020). In order to explain this possible increased frequency of NPD in these children, different possible risk factors have been implicated, such as auto-antibodies and drugs assumed during pregnancy and Azathioprine (AZA). A recent literature review regarding therapy with AZA during pregnancy concluded that it does not seem to increase the risk of congenital abnormalities in the offspring, but more long-term studies are needed to analyze the association with NPD in children exposed *in utero*, while considering all the potential confounding factors including maternal disease and familiar, social and economic context (Belizna et al., 2020).

In particular, one study involving 60 children (age range: 3.4–9.2 years) born to 38 SLE mothers found an association between AZA treatment during pregnancy and special education requirement in the offspring: seven out of 13 children exposed *in utero* to AZA required special educational services. This support was requested mainly for language delays (23.3%), dyslexia (5%) and ADHD (5%) (Marder et al., 2013). Another study showed normal intelligence levels and neurological physical examination in a cohort of 40 children born to mothers with positive aPL and a diagnosis of SLE and/or APS, systematically evaluated by a child neurology-psychiatrist (Nalli et al., 2017). A diagnosis of LD was present in 19% of school-aged children, all born to mothers with positive aPL with three positive tests (triple aPL profile); none of seven children exposed *in utero* to AZA had ND or LD. Moreover, in a recent multicentre Italian survey involving women in reproductive age with different rheumatic diseases, no association was found between the reported presence of children NPD and *in utero* exposure to maternal auto-antibodies or drugs, including AZA (Lazzaroni et al., 2017).

TABLE 3 | Univariate analysis comparing children with NPD (n = 11) to children without NPD (n = 81), born to the 92 SLE pregnancies included.

	NPD present	NPD absent	*p*-value
Maternal characteristics			
Age at SLE onset (years), mean (SD)	22.1 (6.5)	23.3 (6.5)	0.745
Caucasian ethnicity	11/11 (100.0)	80/81 (93.8)	1.000
Renal involvement	7/11 (63.6)	57/81 (70.4)	0.730
Concomitant autoimmune diseases	7/11 (63.6)	30/81 (37.0)	0.110
Antiphospholipid syndrome	3/11 (36.4)	9/81 (11.1)	0.721
Sjögren's syndrome	1/11 (9.1)	8/81 (9.9)	1.000
Rheumatoid arthritis	0/11 (0.0)	1/81 (1.2)	1.000
Autoimmune thyroiditis	1/11 (9.1)	7/81 (8.6)	1.000
Pregnancies characteristics			
Age at pregnancy (years), mean (SD)	31.8 (3.2)	32.20 (5.0)	0.762
Disease duration at the beginning of pregnancy (years), mean (SD)	9.3 (5.6)	9.15 (6.1)	0.942
Disease flare during pregnancy	0/11 (0.0)	13/81 (16.0)	1.000
Renal	0/11 (0.0)	9/81 (11.1)	1.000
Cutaneous	0/11 (0.0)	3/81 (3.7)	1.000
Neurologic	0/11 (0.0)	1/81 (1.2)	1.000
Articular	0/11 (0.0)	1/81 (1.2)	1.000
Antiphospholipid antibodies positivity	3/11 (36.4)	21/81 (25.9)	1.000
Triple positivity	2/11 (18.2)	4/81 (4.9)	0.150
Double positivity	0/11 (0.0)	7/81 (8.6)	1.000
Single positivity	1/11 (9.1)	10/81 (12.3)	0.684
Anti-ENA positivity	8/11 (72.7)	46/81 (56.8)	0.347
Anti-Ro/SSA positivity	2/11 (18.2)	25/81 (30.9)	0.498
Maternal treatment during pregnancy			
Corticosteroids	8/11 (72.7)	64/81 (79.0)	0.285
Azathioprine	3/11 (36.4)	24/81 (29.6)	1.000
Hydroxychloroquine	8/11 (72.7)	39/81 (48.1)	0.511
Cyclosporine-A	2/11 (18.2)	7/81 (8.74)	0.333
Children's characteristics			
Male sex	7/11 (63.6)	37/81 (45.7)	0.541
Birth weight (g), mean (SD)	2972.7 (389.8)	2850.1 (558.5)	0.933
Gestational age (weeks), mean (SD)	37.92 (2.2)	36.84 (2.2)	0.336
Small for gestational age	2/10 (20.0)	5/79 (6.3)	0.176
Preterm birth (<37th weeks)	0/11 (0.0)	25/81 (30.9)	0.169
Severe preterm birth (<34th weeks)	0/11 (0.0)	6/81 (7.4)	0.579

NPD, neuropsychiatric disorders. Results are presented as n/n available data (%), except otherwise indicated.

The present study was designed as case-control and the instrument to collect data concerning the long-term neuropsychiatric outcome of the children was a telephone survey, in which SLE mothers were asked to report diagnosis of NPD only when certified by a pediatric neurology or psychiatrist. The two groups of pregnancies were matched in terms of renal involvement, immunologic profile (especially aPL), maternal age at pregnancy and age of the children at the time of the study. Considering the possible influence of all these factors on the gestational outcome and health status of the children born from these pregnancies, the homogeneity of these two groups allowed to evaluate the effects of *in utero* exposure to AZA as an independent factor.

Moreover, the mean age of the 92 children at the time of the study was 14.0 ± 6.20 years, significantly higher as compared to previous studies. This is very relevant to the correct estimation of the frequency of NPD and in particular LD, that can be diagnosed with certainty only during school years (Association, 2013).

In our cohort of 92 children, 11 cases of NPD were observed: 3/27 among those exposed to AZA and 8/65 among those not exposed to AZA, without any significant difference between the two groups (11.1% vs. 12.3%; *p*-value: 1.000). The frequency of ND and particularly LD, was higher in children not exposed to AZA, although without statistically significant difference.

Pregnancies in the group of cases and controls were comparable in terms of different characteristics, including the frequency of obstetric complications and particularly of preterm birth (<37th weeks) and severe preterm birth (<34th weeks), as well as the immunological profile (rate of anti-Ro/SSA and aPL positivity) and frequency of total flares, including renal flares. Only the frequency of cutaneous flares and corticosteroids use was higher in pregnancies treated with AZA as compared to controls, with a higher mean corticosteroid dosage, although not statistically significant (39.7 vs. 26.9 mg of weekly prednisone-equivalent dosage, *p*: 0.128).

By comparing the 11 children with NPD with the other 81 without, we did not observe any difference in terms of maternal disease, pregnancy complication or treatment, nor the neonatal outcome of the children. Importantly, we did not observe an association between prematurity and NPD and the rate of preterm delivery reported in our cohort (27.2%) reflects what previously reported by literature on SLE pregnancies (23–28%) (Lazzaroni et al., 2016).

Regarding the specific diagnosis of NPD, none of the children included in the study showed the presence of autism spectrum

disorders (ASD), although a previous study large reported a higher prevalence in 719 SLE offspring as compared to 8,493 matched controls (1.4% [95% confidence interval (95% CI) 0.8–2.5] vs. 0.6% [95% CI 0.5–0.8]) (Vinet et al., 2015).

In our cohort the frequency of ADHD (2/92, 2.17%) was similar to that previously reported in a systematic review (1–5%) (Yengej et al., 2017), and even lower than that reported in general pediatric population (7.2% according to a recent meta-analysis) (Thomas et al., 2015). Concerning the language delay, the frequency was also lower than that reported in the general pediatric population in Italy (3–4%) (Cipriani et al., 2002), while previous data in children born to SLE mothers are lacking.

The frequency of LD certified by children neurologists and psychiatrist is 6.52% in this study, that is only slightly higher than that estimated in the general pediatric population (around 4.5% in children in scholar age), and lower than that previously reported in the offspring of SLE mothers (21.4–26%) (Yengej et al., 2017). Dyslexia was the most frequent LD, with a frequency similar to the general population (2.5–5%) and inferior to what previously reported for SLE offspring (14.3–21.6%) (Yengej et al., 2017). No cases of LD were observed in the group of children exposed *in utero* to AZA.

Epilepsy was also less frequent (1/92, 1.1%) then previously reported in children born to SLE and/or APS patients in a multidisciplinary study (10%) (Nalli et al., 2017), and similar to general Italian pediatric population in which it was estimated around 3% (Banerjee et al., 2009), although the relatively small sample size in our study does not allow to adequately compare this prevalence.

Altogether, these data suggest that the long-term neuropsychiatric outcome of the children born to SLE mothers seems to be reassuring, with an estimated frequency of NPD (certified by expert clinicians) similar to the general pediatric population. Only LD showed a slightly increased frequency as compared to general pediatric population. Importantly, *in utero* exposure to AZA does not seem to be associated with the development of NPD. Moreover, no other specific risk factors associated with these pathological outcomes emerged from this study, including autoantibodies, disease activity during pregnancy, obstetric complications or prematurity.

Regarding the role of autoantibodies, particularly aPL, fetal brain was suggested to be one of the main target organs of aPL in APS-mice (Bertolaccini et al., 2016). In our cohort the presence of aPL was relatively low (26.1%), even if equally distributed between cases and controls. Moreover, when we compared the two groups of children with NPD to those without NPD, we found no significant difference in terms of aPL exposure, even if a slightly increased frequency of triple aPL positivity was present in the group of affected children.

The limitations of the present study are: 1) the relatively small sample size, although derived from the historical cohorts of two referral centers for SLE; 2) a wide time interval (1987–2014) during which the management of SLE pregnancies has evolved and improved; on the other hand, we should consider that this factor was normalized by the match of cases and controls by children's age; 3) the use of a telephone survey, implying the possibility of a recall bias especially for older pregnancies, even if only diagnosis certified by neuropsychiatrists were considered.

Moreover, it should be underlined that is difficult to demonstrate the association of one single drug with the development of NPD, which are very complex conditions with a multifactorial pathogenesis. Particularly, we cannot exclude that other factors not considered in our analysis cohort could have contributed to NPD, such as socio-demographic and educational levels or the exposure to other medications not specifically related to SLE. This is the case for example of acetaminophen, a drug that has been traditionally considered as safe during pregnancy, so that pregnant patients may miss to report its use to their Physicians. However, a study published in 2016 highlighted the possibility that children exposed to acetaminophen prenatally could be at increased risk of multiple behavioral difficulties (Stergiakouli et al., 2016). In our cohort, even if the use of acetaminophen was not systematically recorded, we can assume that the chance for a continuous use of this drug is rather low, since only one patient had an articular flare during pregnancy and was treated with corticosteroids.

In conclusion, this case-control study of children born to SLE patients, who had been prospectively followed during pregnancy, did not highlight any specific pattern of NPD, both in children exposed and not exposed to AZA. The practical message is very relevant to the clinicians who take care of SLE patients during childbearing age. At this moment, there are no solid data supporting an association between the use of AZA during pregnancy and the development of NPD in exposed children. Therefore, there is no need to give up AZA as therapeutic choice during pregnancy, as there are, on the other hand, data supporting it as a key-drug in the management of SLE pregnancies of patients with previous severe organ involvement (e.g., renal, neurologic) to minimize the risk of flare (Skorpen et al., 2016; Andreoli et al., 2017; Sammaritano et al., 2020). Large multicentre prospective studies are needed to confirm these findings and to explore other factors contributing to NPD, particularly those not specifically related to SLE.

Anyway, it is important to inform SLE mothers about possible symptoms of NPD in their children, and in particular LD, and to invite them to seek for a specialist evaluation in case of doubts. A chronic disabling condition during childhood and/or youth can have a major impact on family life and global children's health, therefore early diagnosis and treatment are crucial. The inclusion of a child Psychiatrist-Neurologist in the multidisciplinary team dedicated to SLE patients and their families could be proposed as a future perspective for the holistic management of these young women.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitato Etico di Brescia. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

M-GL, LA, AT, GM, and FF designed the study. M-GL, LA, CN, and ID organized the database. M-GL, LA, AT, CN, FC, ID, FT, VB, GM, and FF evaluated the patients and fulfilled the database. M-GL, ID, FC, LA, AT, EF, JG, FT, VB, and JM wrote the manuscript. All authors reviewed the manuscript draft, read and approved the submitted version.

REFERENCES

Abisror, N., Mekinian, A., Lachassinne, E., Nicaise-Roland, P., De Pontual, L., Chollet-Martin, S., et al. (2013). Autism spectrum disorders in babies born to mothers with antiphospholipid syndrome. *Semin. Arthritis Rheum.* 43 (3), 348–351. doi:10.1016/j.semarthrit.2013.07.001

Andreoli, L., Crisafulli, F., and Tincani, A. (2017) Pregnancy and reproductive aspects of systemic lupus erythematosus. *Curr. Opin. Rheumatol.* 29, 473–479.doi:10.1097/BOR.0000000000000415

Andreoli, L., Lazzaroni, M. G., Carini, C., Dall'Ara, F., Nalli, C., Reggia, R., et al. (2019). "Disease knowledge index" and perspectives on reproductive issues: a nationwide study on 398 women with autoimmune rheumatic diseases. *Joint Bone Spine* 86, 475–481.doi:10.1016/j.jbspin.2018.12.002

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders (dsm-5®)*. American Psychiatric Pub.

Banerjee, P. N., Filippi, D., and Hauser, W. A. (2009). The descriptive epidemiology of epilepsy—a review. *Epilepsy Res.* 85, 31–45.doi:10.1016/j.eplepsyres.2009.03.003

Belizna, C., Meroni, P. L., Shoenfeld, Y., Devreese, K., Aliotaj-Reig, J., Esteve-Valverde, E., et al. (2020). Utero exposure to azathioprine in autoimmune disease. Where do we stand? *Autoimmun. Rev.* 19 (9), 102525.doi:10.1016/j.autrev.2020.102525

Bertolaccini, M. L., Contento, G., Lennen, R., Sanna, G., Blower, P. J., Ma, M. T., et al. (2016). Complement inhibition by hydroxychloroquine prevents placental and fetal brain abnormalities in antiphospholipid syndrome. *J. Autoimmun.* 75, 30–38.doi:10.1016/j.jaut.2016.04.008

Brucato, A., Astori, M. G., Cimaz, R., Villa, P., Destri, M. L., Chimini, L., et al. (2006). Normal neuropsychological development in children with congenital complete heart block who may or may not be exposed to high-dose dexamethasone in utero. *Ann. Rheum. Dis.* 65, 1422–1426.doi:10.1136/ard.2005.049866

Cipriani, P., Chilosi, A., Pfanner, L., Villani, S., and Bottari, P. (2002). Il ritardo del linguaggio in età precoce: profili evolutivi ed indici di rischio. O Capirci, MC Caselli (a cura di), Indici di rischio nel primo sviluppo del linguaggio: ricercar, clinica. *Educazione*, 95–108.

Gergianaki, I., Bortoluzzi, A., and Bertsias, G. (2018). Update on the epidemiology, risk factors, and disease outcomes of systemic lupus erythematosus. *Best Pract. Res. Clin. Rheumatol.* 32, 188–205.

Hochberg, M. C. (1997). Updating the american college of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 40, 1725.doi:10.1002/1529-0131(199709)40:9<1725::AID-ART29>3.0.CO;2-Y

Lazzaroni, M. G., Dall'Ara, F., Fredi, M., Nalli, C., Reggia, R., Lojacono, A., et al. (2016). A comprehensive review of the clinical approach to pregnancy and systemic lupus erythematosus. *J. Autoimmun.* 74, 106–117.doi:10.1016/j.jaut.2016.06.016

Lazzaroni, M. G., Nalli, C., Andreoli, L., Carini, C., Rodrigues, M., Dall'Ara, F., et al. (2017). Long-term follow-up of 320 children born to mothers with systemic autoimmune diseases: a multicentre survey from 24 rheumatology centers in Italy. *Arthritis Rheumatology* S69.

Marder, W., Ganser, M. A., Romero, V., Hyzy, M. A., Gordon, C., McCune, W., et al. (2013). Utero azathioprine exposure and increased utilization of special educational services in children born to mothers with systemic lupus erythematosus. *Arthritis Care Res.* 65, 759–766.doi:10.1002/acr.21888

Marder, W., Romero, V. C., Ganser, M. A., Hyzy, M. A., Gordon, C., McCune, W., et al. (2014). Increased usage of special educational services by children born to mothers with systemic lupus erythematosus and antiphospholipid antibodies. *Lupus Sci. Med.* 1. doi:10.1136/lupus-2014-000034

McAllister, D. L., Kaplan, B. J., Edworthy, S. M., Martin, L., Crawford, S. G., Ramsey-Goldman, R., et al. (1997). The influence of systemic lupus erythematosus on fetal development: cognitive, behavioral, and health trends. *J. Int. Neuropsychol. Soc.* 3, 370–376. doi:10.1017/s1355617797003706

Mekinian, A., Lachassinne, E., Nicaise-Roland, P., Carbillon, L., Motta, M., Vicaut, E., et al. (2013). European registry of babies born to mothers with antiphospholipid syndrome. *Ann. Rheum. Dis.* 72, 217–222.doi:10.1136/annrheumdis-2011-201167

Motta, M., Chirico, G., Rebaioli, C. B., Faden, D., Lojacono, A., Allegri, F., et al. (2006). Anticardiolipin and anti-beta2 glycoprotein i antibodies in infants born to mothers with antiphospholipid antibody-positive autoimmune disease: a follow-up study. *Am. J. Perinatol.* 23, 247–252.doi:10.1055/s-2006-939533

Nalli, C., Galli, J., Lazzaroni, M. G., Andreoli, L., Fazzi, E., and Tincani, A. (2020). Long-term outcome of children born from mothers with autoimmune diseases. *Best Pract. Res. Clin. Obstet. Gynaecol.* 64, 107–116.doi:10.1016/j.bpobgyn.2019.11.003

Nalli, C., Iodice, A., Andreoli, L., Galli, J., Lojacono, A., Motta, M., et al. (2017). Long-term neurodevelopmental outcome of children born to prospectively followed pregnancies of women with systemic lupus erythematosus and/or antiphospholipid syndrome. *Lupus* 26, 552–558.doi:10.1177/0961203317694960

Ross, G., Sammaritano, L., Nass, R., and Lockshin, M. (2003). Effects of mothers' autoimmune disease during pregnancy on learning disabilities and hand preference in their children. *Arch. Pediatr. Adolesc. Med.* 157, 397–402.doi:10.1001/archpedi.157.4.397

Sammaritano, L. R., Bermas, B. L., Chakravarty, E. E., Chambers, C., Clowse, M. E., Lockshin, M. D., et al. (2020). American College of Rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Care Res.* 72, 461–488.doi:10.1002/acr.24130

Skorpen, C. G., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., et al. (2016). The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheum. Dis.* 75 (5), 795–810.doi:10.1136/annrheumdis-2015-208840

Stergiakouli, E., Thapar, A., and Smith, G. D. (2016). Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. *JAMA Pediatrics* 170, 964–970.doi:10.1001/jamapediatrics.2016.1775

Thomas, R., Sanders, S., Doust, J., Beller, E., and Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics* 135, e994–e1001.doi:10.1542/peds.2014-3482

Urowitz, M., Gladman, D., MacKinnon, A., Ibanez, D., Bruto, V., Rovet, J., et al. (2008). Neurocognitive abnormalities in offspring of mothers with systemic lupus erythematosus. *Lupus* 17, 555–560.doi:10.1177/0961203308089326

Vinet, É., Pineau, C. A., Clarke, A. E., Scott, S., Fombonne, É., Joseph, L., et al. (2015). Increased risk of autism spectrum disorders in children born to women with systemic lupus erythematosus: results from a large population-based cohort. *Arthritis Rheumatol.* 67, 3201–3208. doi:10.1002/art.39320

Yengej, F. A. Y., van Royen-Kerkhof, A., Derksen, R. H., and Fritsch-Stork, R. D. (2017). The development of offspring from mothers with systemic lupus erythematosus. A systematic review. *Autoimmun. Rev.* 16, 701–711.doi:10.1016/j.autrev.2017.05.005

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co-authorship with several of the authors LA and AT.

frontiers in Pharmacology

SYSTEMATIC REVIEW
published: 20 January 2021
doi: 10.3389/fphar.2020.612259

Inflammasome Targeted Therapy in Pregnancy: New Insights From an Analysis of Real-World Data From the FAERS Database and a Systematic Review

Carla Carnovale[1]†, Enrico Tombetti[2]*†, Vera Battini[1], Faizan Mazhar[1], Sonia Radice[1], Mariangela Nivuori[3], Enrica Negro[3], Silvia Tamanini[3] and Antonio Brucato[2]*

[1]Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences L. Sacco, "Luigi Sacco" University Hospital, Università di Milano, Milan, Italy, [2]Department of Biomedical and Clinical Sciences, Università di Milano, Fatebenefratelli Hospital, Milan, Italy, [3]Internal Medicine, Fatebefratelli Hospital, Milan, Italy

OPEN ACCESS

Edited by:
Cecilia Beatrice Chighizola, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Ariela Hoxha, San Bortolo Hospital, Italy
Gabriele Simonini, University of Florence, Italy

***Correspondence:**
Carla Carnovale
carla.carnovale@unimi.it

†These authors have contributed equally to this work.

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: 30 September 2020
Accepted: 16 December 2020
Published: 20 January 2021

Citation:
Carnovale C, Tombetti E, Battini V, Mazhar F, Radice S, Nivuori M, Negro E, Tamanini S and Brucato A (2021) Inflammasome Targeted Therapy in Pregnancy: New Insights From an Analysis of Real-World Data From the FAERS Database and a Systematic Review. Front. Pharmacol. 11:612259. doi: 10.3389/fphar.2020.612259

The published experience with biologics in childbearing age with autoimmune and inflammatory diseases mainly deals with the use of TNFα inhibitors (TNFα-i). Limited data are available for biologics targeting other cytokines or immunocompetent cells, especially for the inflammasome targeted therapy including IL-1 inhibitors and colchicine. We conducted a nested case-control study by using the US Food and Drug Administration Adverse Event Reporting System database aimed at quantifying the association between the use of IL-1 inhibitors/colchicine in pregnant women and the occurrence of maternal/fetal adverse effects. The reporting odds ratio was used as a measure of disproportional reporting. From the total cohort (40,033 pregnant women), we retrieved 7,620 reports related to neonatal AEs, 2,889 to fetal disorders, 8,364 to abortion, 8,787 to congenital disorders, and 7,937 to labor/delivery complications. Inflammasome-targeted drugs did not present any disproportionate reporting for all these clusters of AEs. TNFα-i confirmed their safety during pregnancy with aROR < 1 for all clusters of AEs except for labor complications. Finally, we performed a systematic review of the current literature. Data from the eligible studies (12 observational studies and 6 case reports; yielding a total of 2,075 patients) were reassuring. We found no major safety issues on malformations risk of inflammasome targeted therapies in pregnancy. However, due to limited data, the routine use of these agents should be considered in pregnancy only if risk benefit assessment justifies the potential risk to the fetus.

Keywords: pregnancy, pharmacovigilance, inflammasome targeted therapy, IL-inhibitors, colchicine, pharmacovgilance

INTRODUCTION

In the past 2 decades, the number of women in childbearing age with autoimmune and inflammatory diseases has significantly increased, in parallel with some concerns on the safety of biological drugs used to treat these clinical conditions. A huge number of therapeutic options have become available, which may ensure optimal control of disease activity and markedly ameliorate patients' quality of life.

Despite the therapeutic armamentarium to manage pregnant women with systemic autoimmune rheumatic diseases (SARDs) includes a variety of biological agents, scant data are available concerning their use during reproduction and pregnancy, especially in long-term studies (Østensen et al., 2008; Østensen et al., 2015).

Biologics have firstly become available about 20 years ago. Since then, the published experience with biologics during pregnancy mainly deals with the use of TNFα inhibitors (TNFα-i) (Flint et al., 2016; Skorpen et al., 2016; Østensen, 2017); data from a growing number of publications on the use of TNFα-i pregnant women with most autoimmune diseases is reassuring (Smeele and Dolhain, 2019).

In contrast, pregnancy experience of exposure to other monoclonal antibodies targeting cytokines or immunocompetent including CD20 (rituximab), interleukin (IL)-6 receptors (tocilizumab), IL-17A (secukinumab) and nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) inflammasome, has been limited to conference abstracts or simple case reports (Komaki et al., 2017). With regard to therapy of NLRP3-associated diseases, three biologic agents blocking IL-1 are available such as the neutralizing IL-1β antibody canakinumab, the recombinant IL-1 receptor antagonist anakinra, and the soluble decoy IL-1 receptor rilonacept (Dinarello and van der Meer, 2013; Zahid et al., 2019; Klein et al., 2020).

These agents have been used during pregnancy only recently, starting from mothers that required maintenance of biologic therapy to control the undelaying condition. However, the need of a prolonged drug administration during gestation raises many controversial issues about the effects of *in utero* exposure to these agents on the fetus/maternal health. Biologic agents are increasingly used and thus long-term data on the effect of these therapies on fetus development and maternal outcomes would be highly necessary. Prospective registries, some of which are already in place, are intended to serve at the purpose but their data are not available yet. Alternatively, spontaneous reporting systems represent a valuable source of information in frail populations, such as pregnant women. Despite the intrinsic limitations, data-mining of adverse drug reaction (ADR) reports allow to obtain real word data about the safety/efficacy profile of specific drugs, to compare therapeutic options, and gain insight on potential mechanisms of ADRs (Gentili et al., 2018; Perrotta et al., 2019).

In the past decades, no pharmacovigilance studies using spontaneous reporting system database specifically address the inflammasome targeted therapy potential risk of harm in pregnant women or the outcomes in their infants. We thus conducted a case-control study by using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database aimed at quantifying the association between the use of inhibitors of the NLRP3 inflammasome in pregnant women and the occurrence of maternal and fetal adverse effects. Finally, in view of the growing number of studies on this issue, we performed a systematic review of the current literature to include and discuss real-world data, thus contributing to fill the knowledge gaps regarding safe and effective use of new biological drugs in pregnancy.

MATERIALS AND METHODS

US Food and Drug Administration Adverse Event Reporting System Analysis: Data Source and Study Design

In order to appropriately estimate the incidence of pregnancy and neonatal adverse events (AEs) after the administration of inflammasome-targeted drugs, an analysis of the FAERS® has been conducted. FAERS® is an online database maintained by FDA that collects every adverse drug reaction (ADR) report submitted in the US territory and every serious ADR report filed in all 150 countries enrolled in the Program for International Drug Monitoring (PIDM) established by the World Health Organization (WHO).

In FAERS®, healthcare professionals, patients and marketing authorization holders may submit ADR reports in the form of Individual Case Safety Reports (ICSRs). FAERS® employs the latest version of the Medical Dictionary for Regulatory Activities (MedDRA®) in order to properly encode every ADR and WHO Anatomical Therapeutic Chemical (ATC) codes to standardize drug nomenclature.

ICSRs provide administrative information (country, type of report, qualification of the reporter), patient demographics (gender, age, weight), adverse events (seriousness of the ADR, date of onset reaction, outcome), information about drug therapy (drug name, drug start and stop dates, time to onset, dose, indication, dechallenge and rechallenge), but the level of completeness of information varies from case to case (Sakaeda et al., 2013). As the number of safety reports sent to the FDA annually is continuously expanding, the database is largely used to detect novel drug-related safety events (Carnovale et al., 2019a; Carnovale et al., 2019b; Mazhar et al., 2019; Pozzi et al., 2019).

Data Acquisition and Data Processing

This study was designed as a nested case-control study and data were downloaded from the FAERS Public Dashboard (FDA Public Dashboard, 2020). The base cohort consisted of all cases involving any AEs occurred during pregnancy (search terms: "complication of pregnancy"; "Exposure during pregnancy"; "Fetal exposure during pregnancy"; "Maternal exposure during pregnancy").

The study period covered the first quarter of 2010 to the first quarter of 2020.

Duplicate records were detected and deleted accordingly as previously described (Carnovale et al., 2019; Mazhar et al., 2019). In order to reduce the risk of a misleading relationship between drugs and AEs, only reports entered by healthcare professionals were eligible for the final cohort.

Definition of Cases and Controls

Cases were defined as all Individual Case Safety Reports (ICSRs) where inflammasome-targeted drugs were reported

as suspect drug. We then used the Standardized MedDRA Queries (SMQ) related to the group "Pregnancy and neonatal topics" to identify the risk of particular clusters of AEs in our cases. To find ICSRs of interest (*i.e.,* cases reporting any maternal and/or fetal outcome following the use anti-IL drugs/colchicine) in FAERS database, we used the following SMQs: congenital, familial and genetic disorders; fetal disorders; neonatal disorders; termination of pregnancy and risk of abortion; pregnancy, labor and delivery complications and risk factors (excl. abortions and stillbirth) (Introductory Guide for Standardised MedDRA Queries, 2020).

Statistical Analyses

Descriptive analysis was performed for cases and non-cases, in terms of age, male sex (new-borns' ICSR) and the presence of other co-suspect drugs.

To identify signals of disproportionate reporting (SDR) for pregnancy and neonatal outcomes in association with inflammasome-targeted drugs, we used the reporting odds ratio (ROR) as a measure of disproportional reporting, which estimates the frequency of an event of interest with the tested drugs compared with the other drugs. SDR were detected when the number of reports was higher than three and ROR–95% CI was greater than one. We calculated the adjusted ROR (aROR) by using multivariate logistic regression analysis adjusted for the presence of co-suspects, that was considered a potential confounding factor.

Sub-analysis was then performed to compare anti-IL1 agents and colchicine with TNFα-i, a well-known class of drugs used during pregnancy chronically and safely. We used R software for data tiding and statistical analysis (R core team, 2019).

Systematic Review

Literature Search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Moher et al., 2009) (**Supplementary Table S1**). We searched PubMed/MEDLINE, EMBASE databases up to June 23rd, 2020 with no language restriction. We provided our search strategy for PubMed in the Supplementary material (**Supplementary Material S1**); the search strategy was adapted as needed for each database. In brief, we used two terms: Interleukin 1 Receptor Antagonist/colchicine, and Pregnancy. We combined terms with the Boolean operator "AND".

Eligibility Criteria

Inclusion criteria for the qualitative analysis were: studies enrolling human subjects; studies enrolling pregnant women affected by any clinical conditions treated with any anti-IL drugs/colchicine; studies reporting any maternal and/or fetal outcome following the use anti-IL drugs/colchicine; any type of observational studies and clinical trials; case report/case series.

We excluded: literature reviews; conference proceedings/abstracts and unpublished thesis; studies that did not report outcomes of interest; studies that reported the effect of pregnancy on IL-1 Inhibitor therapies/colchicine rather than vice versa.

We identified additional articles potentially eligible through the reference lists of articles included in our systematic review. We did not contact authors for missing data.

Study Selection

We imported into EndNote all the retrieved references from the final search in order to eliminate duplicate records. We screened the titles and abstracts of potentially eligible papers; whereas, we disregarded the papers deemed highly unlikely to be relevant. Finally, we assessed for eligibility all full-text versions of the remaining articles based on our pre-specified eligibility criteria as previously described. Two independent reviewers (CC and VB) conducted the entire search process. Discrepancies between review authors were resolved by discussion with a third review author (ET) to achieve a decision.

Data Extraction and Synthesis

Data from all included studies were extracted using pre-specified forms. The following relevant information was extracted: study type, study duration, number of subjects, number of women treated with biological agents, number of pregnancies, maternal diagnosis, mean age at conception, drug of interest, dose/scheme, concomitant treatment, any maternal and/or fetal outcome following the use of Interleukin 1 Receptor Antagonists/colchicine (including live birth, miscarriages, early/late/voluntary abortion, fetal death, small for gestation age-SGA, congenital malformation and stillbirth) in pregnant women, type of delivery, week at delivery, APGAR score, and duration of follow-up.

RESULTS

Pharmacovigilance Study

Study Population

Of 11,789,929 ICSRs we retrieved from the FAERS in our period of observation, 40,033 involved maternal, fetal and neonatal reactions. Of these, only 84 (0.2%) reported the drugs of interest as "suspect," i.e., 69 for Anti-IL1 and 15 for colchicine; no reports involved both drugs as "suspect." The mean age between cases and non-cases was similar in the pregnant women (29 ± 6 vs. 31 ± 7 years old) with a range between 15 and 68 years old. Among the 84 cases, 24 ICSRs reported AEs for newborns and the maternal diagnoses mostly reported were "Familial Mediterranean Fever" (11 ICSRs) and "Rheumatological diseases" (14 ICSRs). In 59.5% of cases, more than one suspect drug was reported; 48.5% of non-cases reported co-suspect drugs.

Disproportionality Analysis

The number of cases, the crude and adjusted ROR for each cluster of AEs are presented in **Table 1**. From the total cohort, we retrieved 7,620 reports related to neonatal AEs, 2,889 to fetal disorders, 8,364 to abortion, 8,787 to congenital disorders, and 7,937 to labor/delivery complications.

According to the aROR and 95% CI, inflammasome-targeted drugs did not present any disproportionate reporting for all these

TABLE 1 | Disproportionality analysis of adverse drug reactions spontaneous reporting database FAERS for the identification of Pregnancy and neonatal disorders.

	Cases (n)[a]	Non cases (n)[b]	ROR (95% CI)	aROR (95% CI)[c]
Neonatal disorders (n = 7,620)				
Inflammosome targeted	18	7,602	1.16 (0.67; 1.91)	1.09 (0.62; 1.80)
Anti-IL1	14	7,606	1.08 (0.58; 1.89)	1.06 (0.56; 1.86)
Colchicine	4	7,616	1.55 (0.43; 4.53)	1.20 (0.33; 3.50)
Anti-TNFα	487	7,133	0.67 (0.61; 0.74)[d]	0.74 (0.67; 0.82)[d]
Fetal disorders (n = 2,889)				
Inflammosome targeted	7	2,882	1.17 (0.49; 2.36)	1.11 (0.47; 2.25)
Anti-IL1	6	2,883	1.23 (0.47; 2.61)	1.11 (0.47; 2.25)
Colchicine	1	2,888	—	—
Anti-TNFα	185	2,704	0.71 (0.60; 0.82)[d]	0.76 (0.65; 0.88)**
Labor/delivery complications (n = 7,937)				
Inflammosome targeted	19	7,918	1.18 (0.69; 1.93)	1.18 (0.69; 1.93)
Anti-IL1	17	7,920	1.32 (0.74; 2.23)	1.32 (0.74; 2.24)
Colchicine	2	7,935	—	—
Anti-TNFα	852	7,085	**1.36 (1.25;1.47)[d]**	**1.36 (1.25;1.47)[d]**
Abortion (n = 8,364)				
Inflammosome targeted	19	8,345	1.11 (0.65; 1.80)	1.17 (0.68; 1.91)
Anti-IL1	17	8,347	1.24 (0.70; 2.10)	1.26 (0.71; 2.14)
Colchicine	2	8,362	—	—
Anti-TNFα	770	7,594	1.09 (1.00; 1.18)[e]	1.01 (0.93; 1.10)
Congenital disorders (n = 8,787)				
Inflammosome targeted	20	8,767	1.11 (0.66; 1.80)	1.03 (0.61; 1.68)
Anti-IL1	14	8,773	0.91 (0.48; 1.58)	0.88 (0.47; 1.55)
Colchicine	6	8,781	2.37 (0.80; 6.58)	1.78 (0.60; 4.96)
Anti-TNFα	323	8,464	0.34 (0.30; 0.38)[d]	0.38 (0.33; 0.42)[d]

[a]All Individual Case Safety Reports where the use of inflammasome-targeted therapy/Anti-TNFα drugs during pregnancy were reported as suspect in the occurrence of any maternal/neonatal/fetal disorders.

[b]All Individual Case Safety Reports where the use of inflammasome-targeted therapy/Anti-TNFα drugs during pregnancy were reported as suspect drug in the occurrence of any adverse events.

[c]Adjustment for other co-suspects.

[d]$p < 0.001$.

[e]$p < 0.01$.

In bold: aROR >1.

clusters of AEs. Next, we performed a sub-analysis for individual drugs, including IL-1 inhibitors and colchicine and using TNFα-i as a better-characterized reference. No disproportionate reporting was identified for IL-1 inhibitors and colchicine. TNFα-inhibitors confirmed their safety during pregnancy with aROR <1 for all clusters of AEs except for labor complications.

Systematic Review

Characteristics of the Reviewed Studies

The study selection and screening are presented in the PRISMA flow-chart (**Figure 1**). Of the 1,419 articles retrieved (624 results were from PubMed, and 795 from EMBASE), 18 met the inclusion criteria.

Twelve observational studies and 6 case report/series were eligible for the inclusion in our systematic review (**Table 2**), yielding a total of 2,075 patients. No clinical trials reporting maternal and/or fetal outcome following the use of Interleukin 1 Receptor Antagonists/colchicine in pregnant women were found.

The average maternal age at conception ranges from 20 to 36 years. Of the 553 women treated with drugs of interest during pregnancy, 236 (42.6%) had a diagnosis of Familiar Mediterranean Fever (FMF); 3 (0.5%) of adult-onset Still's disease (AOSD), 7 (1.2%) of Cryopyrin Associated Periodic Syndrome (CAPS), 3 (0.5%) of idiopathic recurrent pericarditis (IRP), and in the remaining cases a mixed cohort of women had various rheumatological diseases (FMF, CAPS, AOSD, Behcet's disease, pericarditis, Cogan Syndrome, Juvenile idiopathic arthritis).

With respect to the type of medication used, 10 studies reported data on colchicine, 6 on anakinra, and 2 on canakinumab. The period from the baseline to the last follow-up varied considerably among the studies with a range from the first trimester to 10 years.

Data on the Use of anti-IL1 Drugs During Pregnancy

No studies reporting maternal and/or fetal outcome following the use of rilonacept were found.

Only a retrospective cohort study (Youngstein et al., 2017) and a case report (Egawa et al., 2017) provided data on the use of canakinumab during pregnancy (**Table 2**); in total, data were available for nine pregnancies; of these, eight completed pregnancies resulted in the normal development of the fetus; only 1 miscarriage in Cogan Syndrome patient was found.

Seven studies reported data on the use of anakinra in pregnant women (in total, data were available for 57 pregnancies).

In the prospective cohort study by Bazzani et al. (2015), only one woman took anakinra during a peri-conception period and gestation; the pregnancy resulted in a voluntary abortion. Data on

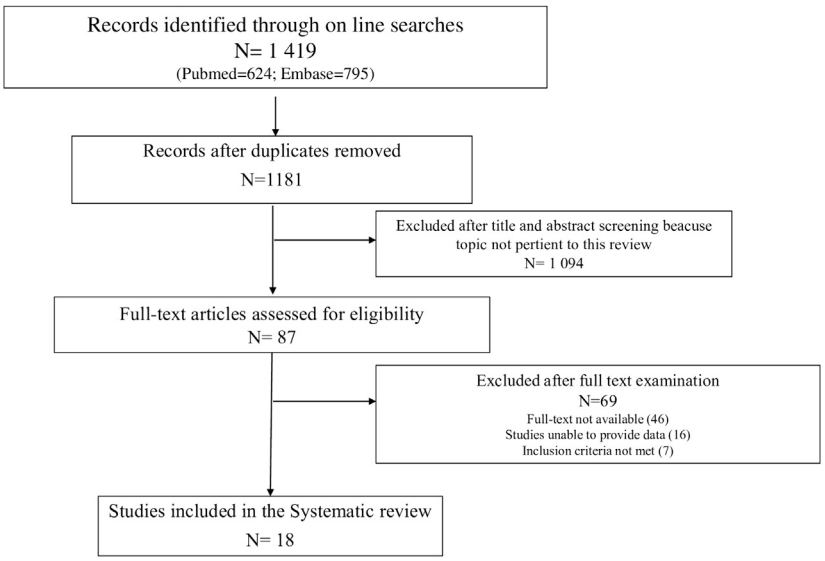


FIGURE 1 | PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram of process of study selection.

case report/series (Fischer-Betz et al., 2011; Berger et al., 2009; İlgen and Küçükşahin, 2017) reported no pregnancy complications or fetal disorders in mothers with AOSD and FMF treated with anakinra (100 mg daily; 1–2 years prior to and through pregnancy and delivery). All pregnancies resulted in the normal development of a fetus.

Five pregnancies with anakinra exposure identified in the study by Smith and Chambers (2018) resulted in full-term singleton live births with no major or long-term complications. Two subjects developed oligohydramnios for unclear reasons.

Of twenty-three anakinra-exposed pregnancies in the retrospective study by Youngstein et al. (2017), 21 resulted in the birth of healthy infants (with follow-up of up to 10 years); one baby with unilateral renal agenesis and ectopic neurohypophysis was also reported. There were no serious neonatal infections.

In the prospective study by Chang et al. (2014) 6 women with CAPS were treated with anakinra throughout the pregnancy; no preterm births or serious pregnancy complications were reported and the miscarriage rates for pregnancies without and with anakinra treatment were 27% and 11%, respectively. One fetus of the twin pregnancy had renal agenesis and died *in utero*.

Despite reassuring findings, the lack of well-controlled studies make data on the use of anakinra in pregnancy difficult to interpret (**Table 3**).

Data on the Use of Colchicine

Of 10 studies involving patients exposed to colchicine for any duration during pregnancy, eight were observational [of these, four were cohort studies (Ehrenfeld et al., 1987; Diav-Citrin et al., 2010; Yazicioğlu et al., 2014; Brucato et al., 2019); 3 case-control (Ben-Chetrit et al., 2010; Dağlar et al., 2016; Iskender et al., 2020); and 1 cross-sectional (Bodur et al., 2020)] and 2 were case report (Tutuncu et al., 2006; Orabona et al., 2020). Except for the study by Ehrenfeld *et al*, the remaining studies have been published recently (range: 2020–2006). Colchicine doses between 1 and 2 mg daily were reported. Two studies included healthy patients in their control groups (n = 116 women) (Ben-Chetrit et al., 2010; Dağlar et al., 2016).

In total, data were available for 1,155 pregnancies exposed to colchicine for any duration during pregnancy.

Of 1,152 pregnancies in women with FMF, 31% resulted in abortions, 14% in miscarriages, 16% in fetal/congenital anomalies, eight in stillbirth, 60 pre-term delivery; nine SGA and 3 preeclampsia.

There were three completed pregnancies in IRP patients, with good maternal/fetal outcomes (Orabona et al., 2020; Brucato et al., 2019). As reported in **Table 3**, findings from studies with control or comparator group reported no difference between the group of women treated with colchicine throughout all pregnancies and healthy women, in terms of miscarriages, early/late abortions, still-birth, fetal/congenital malformations, SGA, pre-term deliveries, and preeclampsia (Ehrenfeld et al., 1987; Ben-Chetrit et al., 2010; Diav-Citrin et al., 2010; Yazicioğlu et al., 2014; Dağlar et al., 2016; Iskender et al., 2020; Bodur et al., 2020). However, the robustness of uncontrolled evidence was poor in the reviewed studies.

Table 4 reported a summary of evidence on the use of Inflammasome target therapies in pregnancy.

DISCUSSION

Available data assessed from the published literature shows that the rates of major congenital deformities and miscarriages for investigated inflammasome target therapies do not differ considerably from those rates in the general population. It

TABLE 2 | Detailed overview of published data on Inflammosome target therapies and evidence for their use during pregnancy.

Id	Study design	Maternal diagnosis	Pregnant treated with drugs of interest/total cohort (no. total pregnancies)	Dose	Mean age at conception (years)	Weeks of gestation; no. of pregnancies: delivery type	APGAR Score	No. Pregnancy outcome in women treated with drugs of interest/control group	Additional relevant data	Follow-up
Brucato et al. (2019)	Retrospective/ prospective cohort	IRP	2/14 (21)	Colchicine 1 mg 5 days/week during all the pregnancy	25	At week 40	nr	2: good maternal outcome	na	1 year after delivery
				Colchicine 1 mg/ daily during all the pregnancy	36	At week 38		2: live birth		
Ben-Chetrit et al. (2010)	Case control	FMF	*Group 1:* 61/ 132 (179)	Colchicine 1.0–1.5 mg daily (throughout all pregnancies)	24.4 ± 3.7[a]	17: CS	nr	16: early abortions 2: late abortions 1: VSD/ASD	The number of early and late abortions, congenital malformations were higher in groups 2 and 3 compared with group 1 but did not reach the level of statistical significance	10 years
			Group 2: 22/ 132 (104)	Colchicine 1.0–1.5 mg daily (during some pregnancies)	23 ± 4.3	5:CS	nr	23: early abortions 3: late abortions 1: died 1: ccenter lip 1: hydronephrosis		
			Group 3: 49/ 132 (197)	Colchicine 1.0–1.5 mg daily (no during pregnancies)	23.2 ± 4.8	18: CS	nr	27: early abortions 4: late abortions 1: Fallot's 1: ccenter lip		
		Healthy women	*Control group:* 84 (312)	na	40.8 ± 11	nr	nr	46: early abortions 6: late abortions 2: major congenital malformations 1: mild muscle weakness		
Bodur et al. (2020)	Cross-sectional	FMF	*Group 1:* 62/ 401 (585)	Colchicine nr (during pregnancy)	na	nr	nr	12: pre-term delivery 13: abortus 8: stillbirth 1: fetal anomaly	Pregnant/neonatal disorders were similar among FMF patients regardless of colchicine use	nr
			Group 2: 339/ 401 (585)	Colchicine free	na	nr	nr	29: pre-term delivery 93: abortus 24: stillbirth 9: fetal anomaly		
Dağlar et al. (2016)	Prospective case control	FMF	*Group 1:* 33 pregnancies	Colchicine 1.5–2 g	25 ± 4.63[b]	21: VD 12: CS	3: Apgar ≤7	7: preterm delivery 1: birth weight <10th percentile 4: NICU admission	No significant differences in preterm delivery (p = 0.73), preeclampsia (p = 1) low Apgar scores (p = 1) and NICU admission (p = 1) between the groups. No cases of fetal chromosomal anomaly or perinatal mortality in either of the groups	From the first trimester to the end of the pregnancies
		Healthy pregnant	*Control group 2:* 32 pregnancies	na	28.5 ± 7.2[c]	21: VD 11: CS	4: Apgar ≤7	1: preeclampsia 7: preterm delivery 1: birth weight <10th percentile 3: NICU admission		

(Continued on following page)

TABLE 2 | (*Continued*) Detailed overview of published data on Inflammosome target therapies and evidence for their use during pregnancy.

Id	Study design	Maternal diagnosis	Pregnant treated with drugs of interest/total cohort (no. total pregnancies)	Dose	Mean age at conception (years)	Weeks of gestation; no. of pregnancies: delivery type	APGAR Score	No. Pregnancy outcome in women treated with drugs of interest/control group	Additional relevant data	Follow-up
Diav-Citrin et al. (2010)	Prospective comparative cohort	FMF (87.3%) Bechet disease (7.5%) or other (5.2%)	*Group 1:* 238 pregnancies	Colchicine 1 mg daily (97%: at least in the first trimester)	29[b] (median)	nr	nr	12: miscarriage 10: major anomalies[c] 32: preterm delivery	The rate of major anomalies, after first-trimester exposure was comparable between the 2 groups $p = 0$ 0.288	nr
		nr	*Group 2:* 964 pregnancies	Counseled for non-teratogenic exposure	30[b] (median)	nr	nr	55: miscarriage 35: major anomalies 51: preterm delivery		
Ehrenfeld et al. (1987)	Prospective cohort	FMF	*Group 1:* 10/23 (28)	Colchicine (throughout the entire period of pregnancy)	nr	nr	nr	2: miscarriage 9: live birth	na	Upto 12 years
			Group 2: 17/25 (24)	Colchicine discontinued before attempting to conceive	nr	nr	nr	2: miscarriage 22: live birth	na	
Iskender et al. (2020)	Prospective case-control	FMF	Group 1: 55/66 (nr)	Colchicine (during pregnancy)	26.9 ± 5.6[b]	17: CS	nr	3: preeclampsia 8: SGA 9: preterm delivery 3: fetal anomaly[d]	Rates of preeclampsia, preterm delivery, SGA neonates and primary caesarean: similar between groups	nr
		Healthy women	Group 2: 11/66 (nr)	Patients non using colchicine	29.2 ± 6.2[b]	4: CS	nr	1: SGA 1: preterm delivery		
Orabona et al. (2020)	Case report	IRP	1 pregnancy	Colchicine 1.5 mg daily (during pregnancy)	30[b]	CS at 38/40 weeks	nr	1: good maternal outcome 1: live birth	Healthy male baby of adequate weight	nr
Tutuncu et al. (2006)	Case report	FMF	1 pregnancy	Colchicine 1.5 mg daily (throughout pregnancy)	20[b]	CS at 38/40 weeks	nr	1: good maternal outcome 1: live birth	Healthy female newborn without congenital anomaly	nr
Yazicioğlu et al. (2014)	Retrospective cohort	FMF	42/50 (50)	Colchicine	29.5 ± 5.1[b]	36.1 ± 4.0 weeks	nr	1: thanatophoric dysplasia	Preterm delivery (p = 0.058), low birth weight (p = 0.416) and congenital anomalies (p = 0.451) were not significantly associated with colchicine therapy	Until delivery
			8/50 (50)	Colchicine free		37.8 ± 1.7 weeks	nr	1: open type neural tube defect		
Bazzani et al. (2015)	Prospective cohort	Rheumatological diseases	1/67 (79)	Anakinra nr (during peri-conception period and/or during gestation)	33 ± 5	na	na	1: voluntary abortion	na	6 months after pregnancy
Berger et al. (2009)	Case report	AOSD	1 pregnancy	Anakinra 100 mg daily (2 years prior to and through pregnancy and delivery)	33[b]	VD at 41/40 weeks	7,8,9	1: live birth 1: good maternal outcome	This is the first report of treatment of AOSD with anakinra during pregnancy	4 months

(Continued on following page)

TABLE 2 | (*Continued*) Detailed overview of published data on Inflammosome target therapies and evidence for their use during pregnancy.

Id	Study design	Maternal diagnosis	Pregnant treated with drugs of interest/total cohort (no. total pregnancies)	Dose	Mean age at conception (years)	Weeks of gestation; no. of pregnancies: delivery type	APGAR Score	No. Pregnancy outcome in women treated with drugs of interest/control group	Additional relevant data	Follow-up
Fischer-Betz et al (2011)	Case series	AOSD	Case 1: 1 pregnancy	Anakinra 100 mg daily (1 year prior to pregnancy and throughout)	27	VD at 39/ 40 weeks	9/9/10	1: live birth 1: good maternal outcome	There were no pathological findings on pediatric examination at discharge	nr
			Case 2: 1 pregnancy	Anakinra 100 mg daily (12/40 onwards)	29	CS at 36/ 40 weeks	8/9/9	1: live birth 1: good maternal outcome	nr	nr
Chang et al. (2014)	Prospective cohort	CAPS	6/9 (24)	Anakinra range: 100–300 mg daily (during pregnancy)	26.4 (range: 19–35)[b]	7: VD 2: CS	nr	1: miscarriage 1: fetal demise of 1 fetus with renal agenesis in twin dichorionic-diamniotic pregnancy	nr	nr
İlgen and Küçükşahin (2017)	Case report	FMF	1 pregnancy	Anakinra 100 mg daily (during pregnancy)	27	CS at 38/ 40 weeks	9,10	1: live birth 1: good maternal outcome	nr	13 months
Smith and Chambers (2018)	Prospective cohort	AOSD (60%) JIA (40%)	5 pregnancies	Anakinra 100 mg daily (during pregnancy)	30.6 (range: 21.0–36.8)[b]	3: VD 2: CS	nr	2: oligohydramnios[e] 3: jaundice 1: tongue tied 1: right hydrocele, heart murmur resolved	Previous exposure throughout her pregnancy to celecoxib[e]	nr
Youngstein et al. (2017)	Retrospective cohort	CAPS (66.6%) FMF (33.3%) Inflammatory illness (16.6%)	7/7 (8)	Canakinumab (during pregnancy)	24 ± 5.1 (range: 16–32)	3: CS 2: VD 2: nr	Range: 9–10	1: miscarriage[§] 7: live birth	Both canakinumab and anakinra. Normal development[§]	Upto 10 years
		CAPS (52.1%) AOSD (17.4%)	23/23 (23)	Anakinra (during pregnancy)	29 (range: 20–38)[b]	7: VD 4: CS	Range: 7–10	1: miscarriage[§] 1: ectopic neurohypophysis; center renal agenesis 22: live birth	nr	
		FMF (13%) TRAPS (8.6%) Pericarditis (4.3%) Cogan Syndrome (4.3%)				2: ID				
Egawa et al. (2017)	Case report	CAPS	1 pregnancy	Canakinumab 150 mg every 8 weeks (during pregnancy)	32	CS	8	1: live birth	First report of the administration of canakinumab during pregnancy in a CAPS patient	1 month after delivery

AOSD, adult-onset Still's disease; CAPS, Cryopyrin Associated Periodic Syndrome; CS, cesarean section; FMF, Familiar Mediterranean Fever; ID, induced delivery; IRP, idiopathic recurrent pericarditis; IVF, in vitro *fertilization; na, not applicable; MWS, muckle-Wells Syndrome; nr, not reported; SGA, Small for gestational age; VD, vaginal delivery; VSD/ASD, ventricular septal defect, atrial septal defect.*

[a]*Age at first pregnancy.*

[b]*Maternal age.*

[c]*Muscular ventricular septal defect, duplex collecting kidney and supraventricular tachycardia.*

[d]*Craniosynostosis; cerebral palsy; VSD; congenital hypothyroidism; urinary reflux; clubfoot; clubfeet; omphalocele; severe microcephaly.*

[e]*Previous exposure throughout her pregnancy to celecoxib, a drug in the NSAID class that has been previously associated with the development of low amniotic fluid levels.*

[§]*patient who received both canakinumab and anakinra in two separate pregnancies both resulting in miscarriage.*

TABLE 3 | Findings of systematic reviews on anakinra and colchicine for each outcome included in the analysis.

OUTCOME	No. of cases in women exposed to Anakinra (% of total pregnancies[a])	No. of cases in the control group (% of total pregnancies)	No. of cases in women exposed to Colchicine (% of total pregnancies[a])	No. of cases in the control group (% of total pregnancies[b])
Miscarriages	3 (5.3)	—	14 (1.2)	57 (2.9)
Abortions	—	—	31 (2.7)	145 (7.3)
Fetal/congenital anomaly	3 (5.3)	—	16 (1.4)	48 (2.4)
SGA	—	—	9 (0.8)	2 (0.1)
Stillbirth	—	—	8 (0.7)	24 (1.2)
Pre-term delivery	—	—	60 (5.2)	88 (4.5)
Voluntary abortion	1 (1.7)	—	—	—
Pre-eclampsia	—	—	3 (0.3)	1 (0.05)

[a]*Total of pregnancies in women treated with drugs of interest (n = 57 and n = 1,155, for anakinra and colchicine group, respectively). For two studies (Bodur et al., 2020; Yazicioğlu et al., 2014), the total number of pregnancies we considered includes women that did not receive the drug therapy; for the study by Iskender et al., as the total number of pregnancies was not available, we considered the total number of pregnant women treated with the drug of interest.*
[b]*Total of pregnancies in the control group (n = 1978).*

should be stressed that from the published evidence, despite their heterogeneousness, no new safety concerns were identified from a total of 18 reports regarding the use of inflammasomes inhibitors during pregnancy. This has been further supported by the analysis of one of the largest spontaneous reporting system databases where we systematically examined the association for all currently clinically approved IL-1 inhibitors with an enormously higher number of reports representing pregnant population (40,033), strengthening the statistical power of the analyses.

Although there is little definitive evidence for the safety of IL-1 targeted therapies in pregnancy, emerging data from prospective birth cohort studies should help inform their use in pregnancy when no other suitable alternative available that can effectively control the maternal disease. Small scale clinical studies are not

TABLE 4 | Brief summary of evidence on or Inflammosome target therapies use in pregnancy.

IL-1 Antagonist	Human data: *drug use throughout pregnancy*
Anakinra recombinant human IL-1 receptor antagonist	10 completed pregnancies in *AOSD* (Berger et al., 2009; Fischer-Betz et al., 2011; Youngstein et al., 2017; Smith and Chambers, 2018) →1 left renal agenesis; 2 jaundice and 1 tongue tied 36 pregnancies in *CAPS* (Chang et al.,2014; Youngstein et al., 2017) → 1 fetal demise of 1 fetus with renal agenesis in twin pregnancy; 1 miscarriage 4 completed pregnancies in *FMF* (Youngstein et al., 2017; İlgen and Küçükşahin, 2017) → normal development 2 completed pregnancies in *JIA* (Smith and Chambers, 2018) → 2 oligohydramnios, 1 jaundice, 1 right hydrocele 1 voluntary abortion in *unspecified rheumatological disease* (Bazzani et al., 2015) 1 completed pregnancy in *IRP* (Youngstein et al., 2017) → normal development 2 completed pregnancies in *TRAPS* (Youngstein et al., 2017) → normal development 1 miscarriage in *Cogan Syndrome* (Youngstein et al., 2017)
Canakinumab human IgG kappa monoclonal antibody to IL-1Beta	5 completed pregnancies in *CAPS* (Youngstein et al., 2017; Egawa et al., 2017) → normal development 2 completed pregnancies in *FMF* (Youngstein et al., 2017) → normal development 1 miscarriage in *Cogan Syndrome* (Youngstein et al., 2017) 1 completed pregnancy in *Un-SAID* (Youngstein et al., 2017) → normal development
Colchicine Alkaloid extracted from plants of the genus Colchicum (autumn crocus)	1152[a] pregnancies in *FMF* (Ehrenfeld et al., 1987; Tutuncu et al., 2006; Ben-Chetrit et al., 2010; Bodur et al., 2020; Diav-Citrin et al., 2010; Yazicioğlu et al., 2014; Dağlar et al., 2016; Iskender et al., 2020) → 31 abortions; 14 miscarriages; 16 fetal/congenital anomalies; 8 stillbirth; 60 pre-term delivery; 9 SGA; 3 preeclampsia 3 completed pregnancy in *IRP* (Brucato et al., 2019; Orabona et al., 2020) → normal development
Rilonacept Dimeric, glycosylated fusion protein composed of the extracellular domains of the interleukin 1 receptor and an accessory protein IL-1-RAcP fused to the Fc domain of human IgG1	No data

AOSD, adult-onset Still's disease; CAPS, Cryopyrin Associated Periodic Syndrome; FMF, Familiar Mediterranean Fever; IRP, idiopathic recurrent pericarditis; JIA, Juvenile idiopathic arthritis; TRAPS, Tumor Necrosis Factor Receptor Associated Periodic Syndrome; Un-SAID, undifferentiated systemic autoinflammatory disorder.
[a]*For two studies (Bodur et al., 2020; Yazicioğlu et al., 2014), the total number of pregnancies we considered includes women that did not receive the drug therapy; for the study by Iskender et al., as the total number of pregnancies was not available, we considered the total number of pregnant women treated with the drug of interest.*

robust enough to answer safety concerns. In real-world, pregnant women take drugs either intentionally or unintentionally. Intentionally because some conditions require treatment during pregnancy, whilst a large proportion of pregnancies are unplanned entails unintentional drugs (Sheffield et al., 2014). Therefore, a constant vigilance of spontaneous reporting systems is essential to guarantee the safety profile of novel or repurposed treatment options. Findings obtained from case/non-case analyses of FAERS showed no potential safety signals for maternal and fetal AEs. These results are in accordance with the emerging evidence from small scale studies assessed in the present review. In FAERS, AEs related to pregnancy and neonatal outcomes are reported more frequently for anti-TNFα than treatments targeting IL-1. This could be explained by the fact that anti-TNFα drugs are the most prescribed treatment in pregnancy because of their safety evidence has already been translated into clinical practice (Flint et al., 2016; Skorpen et al., 2016). Like any epidemiology studies, valid results from case/non-case analyses depends on the classification of events and exposure. Underreporting of ADRs due to "misclassification bias" may explain a smaller number of reports for the comparator drug in case/non-case analyses, and henceforth direction and magnitude of the effect (Carnovale et al., 2019; Mazhar et al., 2019).

Our findings expand on Nguyen et al. (Nguyen at al., 2020) systematic review of 11 studies that investigated the risk of adverse pregnancy and neonatal outcomes associated with non-TNFα inhibitors and disease-modifying anti-rheumatic drugs (DMARDs) in pregnancy. Their findings do not suggest an increased risk associated with non-TNF α inhibitors and DMARDs in pregnancy. Nevertheless, the methods in the two studies are different. We have investigated a range of studies focused on IL-1 inhibitors only and have summed up data on congenital malformation/miscarriages. We have also summarized the pattern of reported major congenital malformations. In the present review, each IL-1 inhibitor was considered separately that can be of additional value if one is interested in specific IL-1 inhibitor drug. Moreover, data on maternal baseline characteristics are also detailed as the underlying maternal conditions are essential factors to be considered as a potential confounder for the pregnancy-related outcomes.

According to EMA guidelines, to rule out a ≥2-fold or ≥10-fold risk of major congenital malformations for medicine use during pregnancy, there is a need of moderate amount of data on pregnant women (between 300 and 1,000 pregnancy outcomes) collected prospectively (EMEA, 2008). This information should be collected from exposed pregnancies to that particular drug during the first trimester. Under this recommendation, the ascertainment of risk on summed up data remains unclear for most of the IL-1 antagonist because of the limited total number of exposures. Although for colchicine it can be concluded that it does not carry a ≥2-fold increased risk of combined major congenital malformations as compared to this risk in the general population which was estimated as 2–5.5% (Egbe et al., 2015). Over the past few years, the approach toward the use of colchicine throughout pregnancy has changed. Older reports and the 2015 ESC Guidelines (Adler et al., 2015) recommended against the use of colchicine during pregnancy due to limited information, while available data suggest that did not raise any concern about the teratogenicity of the drug. No association between an increased rate of adverse maternal/fetal outcomes with the colchicine throughout pregnancy was found in a recent systematic review of the literature (Indraratna et al., 2018).

A recent retrospective review of 34 exposed pregnancies to colchicine (Duman et al., 2019) reported the birth of 23 healthy infants and seven with several problems. Of seven infants with problems, four had congenital heart disease, one had nephrolithiasis, one had an inguinal hernia and one had mortality secondary to respiratory distress. The investigator acknowledged that the causality between colchicine use and the reported malformations was not adequately ascertained. These findings indicate that the influence of colchicine cannot be ruled out completely and should be beard in mind in cases of colchicine use for indications other than FMF or Behcet's disease.

Safety data on IL-1 inhibitors anakinra and canakinumab remain very limited. Reviewed real-word data appear reassuring. In a retrospective study by the International Society for Systemic Auto-inflammatory diseases, 43 pregnancies exposed to IL-1 therapies (canakinumab, n = 14 and anakinra n = 29) from seven countries (Youngstein et al., 2017), were identified. There were no developmental abnormalities with a median follow-up of 18 months. They also reported the outcome of 14 neonates breastfed by mothers taking anakinra (n = 10) or canakinumab (n = 4) for up to 10 months, with no reported serious infections.

Largely reassuring outcomes was also reported in a small case series of seven pregnant women with AOSD treated with anakinra (Fischer-Betz et al., 2011; Smith and Chambers, 2018). Of seven pregnant women, two developed oligo-hydramnios, and one developed pregnancy-induced hypertension while taking anakinra. All the infants were born full-term (range: 36–40 weeks of gestation) and there were no adverse outcomes or major complications. Of the seven mothers, three breastfed their newborns successfully, where two mothers chose to breastfeed while continuing anakinra treatment with no reported adverse outcomes. Chang et al. (2014) described 24 pregnancies in patients with CAPS, reporting a lower miscarriage rate in women on anakinra than in those treated with other drugs (10% vs. 30%) suggesting anakinra use may have a protective effect on pregnancy outcomes for patients with IL-1-driven disease. Due to the scantiness of available data on the safety of IL-1 antagonists during conception, until additional information is available, these agents are not currently recommended during pregnancy and their discontinuation should be considered once pregnancy is confirmed (Sammaritano et al., 2020).

For several reasons, it is difficult to determine the impact of medications on obstetric and neonatal outcomes. In prospective studies, early miscarriages are missed because women are only included when they are pregnant and not in the pre-conception period. Whilst retrospective studies are endangered by publication bias because only women with an abnormal pregnancy are reported (Mitchell et al., 2011; Thorpe et al., 2013). Prospective studies that enroll the women from the phase they actively try to become pregnant would cover the pre-conception phase and provide reliable data. Furthermore, confounding by indication (some diseases cause more miscarriages) and by concomitant drugs can also affect the results.

Large population-based cohort studies from routine healthcare settings are crucial for improving the evidence for the safety of IL-1 treatments during pregnancy. Use of growing number of available electronic health care databases may be valuable strategy to capture information on medicine utilization patterns, and medicine safety when used during pregnancy. However, for future non-RCT studies there is a need to overcome important methodological issues related to methods for quantifying exposures to these drugs and other confounders during the whole of pregnancy and for adjusting for the latter in analyses.

Limitations

The robustness of uncontrolled evidence was poor in the reviewed studies. IL-1/colchicine-exposed women are likely to have other factors at some point in pregnancy as poor pregnancy outcomes are multifactorial, generally, this was not measured and so, could not be adjusted for in uncontrolled studies, making interpretation of these studies' findings difficult. Type of disease and disease activity during pregnancy, co-morbid conditions, and concomitant drug treatments could also have contributed to negative outcomes. In some cases, the information on other outcomes (such as previous births, previous miscarriages, preterm births, ADRs, etc.) was not available. Finally, the use of a pharmacovigilance database has some intrinsic limitations; reporting might be influenced by factors including the notoriety bias, selection bias and under-reporting, which precludes making causal inferences except in unusual circumstances (Faillie 2019).

CONCLUSION

Despite limitations, no major safety issues were reported and no increasing trend could be identified in the reported malformations risk of biological IL-1 therapies in pregnancy. Colchicine appears to be compatible with pregnancy. Though these provide no suggestion that biological IL-1 treatments might be harmful, however, due to limited total number of exposed pregnancies the use of these agents in the clinical practice should be considered in pregnancy only if the risk benefit assessment of maintaining disease control justifies the potential risk to the fetus. These findings contribute additional evidence to inform treatment decision making for patients with IRD during pregnancy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct and intellectual contribution to the work and approved it for publication. CC, and ET conceptualized and designed the study, interpreted the data drafted the manuscript, revised and approved the final manuscript as submitted. VB participated in the conceptualization and design of the study, carried out the initial analyses, revised the manuscript and approved the final manuscript as submitted. FM, SR, MN, EN, ST participated in the interpretation of the data, revised the article, and approved the final article as submitted. AB conceptualized and designed the study, interpreted the data, coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

FUNDING

The Authors received financial support for the publication of this article from the Swedish Orphan Biovitrum (Sobi™).

ACKNOWLEDGMENTS

FM is enrolled in the PhD in Experimental and Clinical Pharmacological Sciences, University of Milano, which supports his fellowship".

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.612259/full#supplementary-material.

REFERENCES

Adler, Y., Charron, P., Imazio, M., Badano, L., Barón-Esquivias, G., Bogaert, J., et al. (2015). 2015 ESC guidelines for the diagnosis and management of pericardial diseases: the task force for the diagnosis and management of pericardial diseases of the European Society of Cardiology (ESC) endorsed by: the European association for cardio-thoracic surgery (EACTS). *Eur. Heart J.* 36 (42), 2921–2964. doi:10.1093/eurheartj/ehv318

Bazzani, C., Scrivo, R., Andreoli, L., Baldissera, E., Biggioggero, M., Canti, V., et al. (2015). Prospectively-followed pregnancies in patients with inflammatory arthritis taking biological drugs: an Italian multicentre study. *Clin. Exp. Rheumatol.* 33 (5), 688–693.

Ben-Chetrit, E., Ben-Chetrit, A., Berkun, Y., and Ben-Chetrit, E. (2010). Pregnancy outcomes in women with familial Mediterranean fever receiving colchicine: is amniocentesis justified? *Arthritis Care Res.* 62 (2), 143–148. doi:10.1002/acr.20061

Berger, C. T., Recher, M., Steiner, U., and Hauser, T. M. (2009). A patient's wish: anakinra in pregnancy. *Ann. Rheum. Dis.* 68 (11), 1794–1795. doi:10.1136/ard.2008.105833

Bodur, H., Yurdakul, F. G., Çay, H. F., Uçar, Ü., Keskin, Y., and Sargın, B. (2020). Familial Mediterranean fever: assessment of clinical manifestations, pregnancy, genetic mutational analyses, and disease severity in a national cohort. *Rheumatol. Int.* 40 (1), 29–40. doi:10.1007/s00296-019-04443-0

Brucato, A., Pluymaekers, N., Tombetti, E., Rampello, S., Maestroni, S., Lucianetti, M., et al. (2019). Management of idiopathic recurrent pericarditis during pregnancy. *Int. J. Cardiol.* 282, 60–65. doi:10.1016/j.ijcard.2019.02.003

Carnovale, C., Mazhar, F., Arzenton, E., Moretti, U., Pozzi, M., Mosini, G., et al. (2019a). Bullous pemphigoid induced by dipeptidyl peptidase-4 (DPP-4) inhibitors: a pharmacovigilance-pharmacodynamic/pharmacokinetic assessment

through an analysis of the vigibase®. *Expet Opin. Drug Saf.* 18 (11), 1099–1108. doi:10.1080/14740338.2019.1668373

Carnovale, C., Mosini, G., Gringeri, M., Battini, V., Mazhar, F., Pozzi, M., et al. (2019b). Interaction between paracetamol and lamotrigine: new insights from the FDA Adverse Event Reporting System (FAERS) database. *Eur. J. Clin. Pharmacol.* 75 (9), 1323–1325. doi:10.1007/s00228-019-02691-4

Chang, Z., Spong, C. Y., Jesus, A. A., Davis, M. A., Plass, N., Stone, D. L., et al. 2014). Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). *Arthritis Rheum.* 66 (11), 3227–3232. doi:10.1002/art.38811

Dağlar, K., Kirbaş, A., Timur, H., Kara, O., Inal, H., Gencosmanoglu, G., et al. (2016). Subclinical inflammation and simple blood parameters in pregnant with familial mediterranean fever. *J. Clin. Anal. Med.* 7 (5), 634–638. doi:10.4328/JCAM.4158

Diav-Citrin, O., Shechtman, S., Schwartz, V., Avgil-Tsadok, M., Finkel-Pekarsky, V., Wajnberg, R., et al. (2010). Pregnancy outcome after in utero exposure to colchicine. *Am. J. Obstet. Gynecol.* 203 (2), 144–146. doi:10.1016/j.ajog.2010.02.063

Dinarello, C. A., and van der Meer, J. W. M. (2013). Treating inflammation by blocking interleukin-1 in humans. *Semin. Immunol.* 25, 469–484. doi:10.1016/j.smim.2013.10.008

Duman, N. C., Karabacak, M., Oglu, M. G. I., Inanc, N., Asik, Z. N. T., Atagunduz, P., et al. (2019). "Colchicine use during pregnancy: case reports," in Annual European Congress of Rheumatology (EULAR), Madrid, Spain, 2019, Vol. 78, 2082–2083. doi:10.1136/annrheumdis-2019-eular.3999

Egawa, M., Imai, K., Mori, M., Miyasaka, N., and Kubota, T. (2017). Placental transfer of canakinumab in a patient with muckle-wells syndrome. *J. Clin. Immunol.* 37 (4), 339–341. doi:10.1007/s10875-017-0389-3

Egbe, A., Uppu, S., Lee, S., Stroustrup, A., Ho, D., and Srivastava, S. (2015). Congenital malformations in the newborn population: a population study and analysis of the effect of sex and prematurity. *Pediatr. Neonatol.* 56 (1), 25–30. doi:10.1016/j.pedneo.2014.03.010

Ehrenfeld, M., Brzezinski, A., Levy, M., and Eliakim, M. (1987). Fertility and obstetric history in patients with familial Mediterranean fever on long-term colchicine therapy. *Br. J. Obstet. Gynaecol.* 94 (12), 1186–1191. doi:10.1111/j.1471-0528. 1987.tb02320. x

EMEA (2008). *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling*, 24. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling_en.pdf (Accessed June 20, 2020). July 2008 EMEA/CHMP/203927/2005.

Faillie, J. (2019). Case-non-case studies: principle, methods, bias and interpretation. *Therapie* 74 (2), 225–232. doi:10.1016/j.therap.2019.01.006

FDA Public Dashboard (2020). Available at: https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis (Accessed June 30, 2020).

Fischer-Betz, R., Specker, C., and Schneider, M. (2011). Successful outcome of two pregnancies in patients with adult-onset Still's disease treated with IL-1 receptor antagonist (anakinra). *Clin. Exp. Rheumatol.* 29 (6), 1021–1023.

Flint, J., Panchal, S., Hurrell, A., van de Venne, M., Gayed, M., Schreiber, K., et al. (2016). BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology.* 55 (9), 1693–1697. doi:10.1093/rheumatology/kev404

Gentili, M., Pozzi, M., Peeters, G., Radice, S., and Carnovale, C. (2018). Review of the methods to obtain paediatric drug safety information: spontaneous reporting and healthcare databases, active surveillance programmes, systematic reviews and meta-analyses. *Curr. Clin. Pharmacol.* 13 (1), 28–39. doi:10.2174/1574884713666180206164634

Götestam Skorpen, C., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., et al. (2016). The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheum. Dis.* 75 (5), 795–810. doi:10.1136/annrheumdis-2015-208840

Indraratna, P. L., Virk, S., Gurram, D., and Day, R. O. (2018). Use of colchicine in pregnancy: a systematic review and meta-analysis. *Rheumatology.* 57, 382–387. doi:10.1093/rheumatology/kex353

Introductory Guide for Standardised MedDRA Queries (2020). Introductory Guide for Standardised MedDRA Queries (SMQs) version 23.0. Available at: https://admin.new.meddra.org/sites/default/files/guidance/file/SMQ_intguide_23_0_English.pdf (Accessed June 20, 2020).

Iskender, D., Kara, O., Ozturk Kaymak, A., Daglar, H. K., Kirbas, A., Iskender, C. T., et al. (2020). Association between basal proteinuria levels and pregnancy outcomes in familial Mediterranean fever. *J. Obstet. Gynaecol.* 40, 1102–1105. doi:10.1080/01443615.2019.1700944

İlgen, U., and Küçükşahin, O. (2017). Anakinra use during pregnancy: report of a case with familial Mediterranean fever and infertility. *Eur. J. Rheumatol.* 4 (1), 66–67. doi:10.5152/eurjrheum.2017.16075

Klein, A. L., Imazio, M., Cremer, P., Brucato, A., Abbate, A., Fang, F., et al. (2020). RHAPSODY investigators. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N. Engl. J. Med.* (Online ahead of print). doi:10.1056/NEJMoa2027892

Komaki, F., Komaki, Y., Micic, D., Ido, A., and Sakuraba, A. (2017). Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor-α use in females with immune mediated diseases; a systematic review and meta-analysis. *J. Autoimmun.* 76, 38–52. doi:10.1016/j.jaut.2016.11.004

Mazhar, F., Pozzi, M., Gentili, M., Scatigna, M., Clementi, E., Radice, S., et al. (2019). Association of hyponatraemia and antidepressant drugs: a pharmacovigilance-pharmacodynamic assessment through an analysis of the US Food and drug administration adverse event reporting system (FAERS) database. *CNS Drugs.* 33, 581–592. doi:10.1007/s40263-019-00631-5

Mitchell, A. A., Gilboa, S. M., Werler, M. M., Kelley, K. E., Louik, C., and Hernández-Díaz, S. (2011). Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. *Am. J. Obstet. Gynecol.* 205 (1), 51–58. doi:10.1016/j.ajog.2011.02.029

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G.The PRISMA Group (2009). Preferred reporting Items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 3 (7), e1000097. doi:10.1371/journal.pmed1000097

Nguyen, A. H., Ahmed, K., Flint, G., and Giles, I. (2020). Systematic review of the safety of non-tumour necrosis factor inhibitor and targeted synthetic drugs in rheumatic disease in pregnancy. *Rheumatology.* 59 (2). doi:10.1093/rheumatology/keaa111.114

Orabona, R., Zanardini, C., Zatti, S., Lojacono, A., Procopio, R., Vizzardi, E., et al. (2020). Onset of idiopathic recurrent pericarditis during pregnancy: successful management with colchicine and intravenous immunoglobulins. *J. Cardiovasc. Med.* 21 (5), 393–395. doi:10.2459/JCM.0000000000000904

Østensen, M., Andreoli, L., Brucato, A., Cetin, I., Chambers, C., Clowse, M. E., et al. (2015). State of the art: reproduction and pregnancy in rheumatic diseases. *Autoimmun. Rev.* 14 (5), 376–386. doi:10.1016/j.autrev.2014.12.011

Østensen, M., Lockshin, M., Doria, A., Valesini, G., Meroni, P., Gordon, C., et al. (2008). Update on safety during pregnancy of biological agents and some immunosuppressive anti-rheumatic drugs. *Rheumatology.* 47 (Suppl 3), 28–31. doi:10.1093/rheumatology/ken168

Østensen, M. (2017). The use of biologics in pregnant patients with rheumatic disease. *Expet Rev. Clin. Pharmacol.* 10, 661–669. doi:10.1080/17512433.2017.1305268

Perrotta, C., Giordano, F., Colombo, A., Carnovale, C., Castiglioni, M., Di Bernardo, I., et al. (2019). Postpartum bleeding in pregnant women receiving SSRIs/SNRIs: new insights from a descriptive observational study and an analysis of data from the FAERS database. *Clin. Ther.* 41 (9), 1755–1766. doi:10.1016/j.clinthera.2019.06.008

Pozzi, M., Carnovale, C., Mazhar, F., Peeters, G. G. A. M., Gentili, M., Nobile, M., et al. (2019). Adverse drug reactions related to mood and emotion in pediatric patients treated for attention deficit/hyperactivity disorder: a comparative analysis of the US Food and drug administration adverse event reporting system database. *J. Clin. Psychopharmacol.* 39 (4), 386–392. doi:10.1097/JCP.0000000000001058.PMID: 31205193

R Core Team (2019). *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing. . Available at: https://www.R-project.org/ (Accessed June 20, 2020).

Sakaeda, T., Tamon, A., Kadoyama, K., and Okuno, Y. (2013). Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci* 10, 796–803. doi:10.7150/ijms.6048

Sammaritano, L. R., Bermas, B. L., Chakravarty, E. E., Chambers, C., Clowse, M. E. B., Lockshin, M. D., et al. (2020). 2020 American College of Rheumatology guideline

for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheum.* 72 (4), 529–556. doi:10.1002/art.41191

Sheffield, J. S., Siegel, D., Mirochnick, M., Heine, R. P., Nguyen, C., Bergman, K. L., et al. (2014). Designing drug trials: considerations for pregnant women. *Clin. Infect. Dis.* 59 (Suppl 7), S437–S444. doi:10.1093/cid/ciu709

Smeele, H. T. W., and Dolhain, R. J. E. M. (2019). Current perspectives on fertility, pregnancy and childbirth in patients with rheumatoid arthritis. *Semin. Arthritis Rheum.* 49 (Suppl 3), S32–S35. doi:10.1016/j.semarthrit.2019.09.010

Smith, C. J. F., and Chambers, C. D. (2018). Five successful pregnancies with antenatal anakinra exposure. *Rheumatology.* 57 (7), 1271–1275. doi:10.1093/rheumatology/key093

Thorpe, P. G., Gilboa, S. M., Hernandez-Diaz, S., Lind, J., Cragan, J. D., Briggs, G., et al. (2013). Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. *Pharmacoepidemiol. Drug Saf.* 22 (9), 1013–1018. doi:10.1002/pds.3495

Tutuncu, L., Atasoyu, E. M., Evrenkaya, R., and Mungen, E. (2006). Familial Mediterranean fever-related nephrotic syndrome and successful full-term pregnancy. *Arch. Med. Res.* 37 (1), 178–180. doi:10.1016/j.arcmed.2005.04.013

Yazicioğlu, A., Turgal, M., Yücel, O., Özyüncü, Ö., and Beksaç, M. S. (2014). Pregnancy outcome in women with familial Mediterranean fever: a retrospective analysis of 50 cases with a 10-year experience. *Arch. Rheumatol.* 29 (2), 94–98. doi:10.5606/ArchRheumatol.2014.3707

Youngstein, T., Hoffmann, P., Gül, A., Lane, T., Williams, R., Rowczenio, D. M., et al. (2017). International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. *Rheumatology.* 56 (12), 2102–2108. doi:10.1093/rheumatology/kex305

Zahid, A., Li, B., Kombe, A. J. K., Jin, T., and Tao, J. (2019). Pharmacological inhibitors of the NLRP3 inflammasome. *Front. Immunol.* 10, 2538. doi:10.3389/fimmu.2019.02538

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Pharmacology

REVIEW
published: 11 February 2021
doi: 10.3389/fphar.2021.621247

Biologics During Pregnancy and Breastfeeding Among Women With Rheumatic Diseases: Safety Clinical Evidence on the Road

Asmaa Beltagy[1,2], *Azin Aghamajidi*[3], *Laura Trespidi*[4], *Wally Ossola*[4] *and Pier Luigi Meroni*[1]*

[1]Istituto Auxologico Italiano, IRCCS, Immunorheumatology Research Laboratory, Milan, Italy, [2]Rheumatology and Clinical Immunology Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt, [3]Department of Immunology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran, [4]Department of Obstetrics and Gynaecology, Fondazione Ca Granda, Ospedale Maggiore Policlinico, Milan, Italy

Females are generally more affected by autoimmune diseases, a fact that underlines the relationship with pregnancy and the safety of anti-rheumatic drugs in pregnancy and lactation. Biologic therapies are increasingly prescribed to treat and maintain remission in a significant number of systemic autoimmune rheumatic diseases. The experience with the use of biologics during gestation is extremely lacking because of the observational nature of the available studies and the difficulty in designing proper clinical trials in pregnancy. Among the studied biologics, more information was published on TNFα inhibitors and, in particular, on their potential passage through the placenta and impact on the fetus. Currently, a fragment of anti-TNFα monoclonal IgG, certolizumab pegol, is considered safe with almost no placental transfer. Subsequent observations are suggesting a comparable safety for the soluble TNFα receptor etanercept. Another biologic, eculizumab, the anti-C5a antibody used to treat complement-mediated microangiopathies, is also considered safe due to the unique engineered IgG2/4κ formulation that limits its passage through the placental barrier. Still, long-term data about children born to women treated with biologics in pregnancy are not attainable. Data on breastfeeding are currently available for several biologics. This article reviews the literature available about which drugs are considered safe during pregnancy and lactation, which are not, and on future prospects.

Keywords: biologics, conception, pregnancy, breastfeeding, rheumatic diseases

OPEN ACCESS

Edited by:
Guilherme Ramires De Jesús, Rio de Janeiro State University, Brazil

Reviewed by:
Emily J. Su, University of Colorado, United States
Niccolò Lombardi, University of Florence, Italy

***Correspondence:**
Pier Luigi Meroni
pierluigi.meroni@unimi.it

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *25 October 2020*
Accepted: *04 January 2021*
Published: *11 February 2021*

Citation:
Beltagy A, Aghamajidi A, Trespidi L, Ossola W and Meroni PL (2021) Biologics During Pregnancy and Breastfeeding Among Women With Rheumatic Diseases: Safety Clinical Evidence on the Road. Front. Pharmacol. 12:621247. doi: 10.3389/fphar.2021.621247

INTRODUCTION

Autoimmune diseases affect around 3%–5% of the population. The prevalence is high for some diseases like rheumatoid arthritis (RA) representing ≈0.5%–1% and low for other diseases like systemic sclerosis (≈0.04%) (Jacobson et al., 1997; Cooper and Stroehla, 2003; Gabriel and Michaud, 2009; Schirmer et al., 2012). Systemic autoimmune rheumatic diseases (SARD) are generally more common in women during reproductive age, with female to male ratio up to 13:1 in diseases like systemic lupus erythematosus (SLE) and Sjogren syndrome, making antirheumatic drug exposure during pregnancy and lactation a frequent issue (Jacobson et al., 1997; Petri, 2002; Fava and Petri, 2019).

Pregnancy and SARD are reciprocally related; a flare in disease activity can occur in pregnancy and disease activity negatively affects pregnancy course and outcome (Andreoli et al., 2019; Giles et al., 2019). Therefore, it is crucial to reach and maintain total or near total remission before and

during pregnancy for good pregnancy outcomes. Conventional drugs sometimes do not to achieve this therapeutic target, and safe drug choices are limited in pregnancy (Kuriya et al., 2011; Götestam Skorpen et al., 2016; Ngian et al., 2016).

The management of SARD has changed significantly with the revolutionary advent of biological disease-modifying antirheumatic drugs (bDMARD). Prescription of biologics to millions of patients with SARD has surged remarkably over the last two decades. Common SARD treated with bDMARDs include RA, SLE, spondyloarthritidis (SpA), juvenile idiopathic arthritis (JIA), and autoinflammatory syndromes. Upgrading treatment to biologics led to better control of disease activity that was considered resistant, improved quality of life, and prevented long-term functional disabilities of many patients with SARD (Shadick et al., 2019).

It is not uncommon to encounter a woman who desires a pregnancy or has unplanned pregnancy while on treatment with biologic therapies. Hence, several queries arise about issues related to the gestational safety and efficacy of this particular treatment. The overall experience with the use of biologics and the quality of evidence is not as strong as it should be since most of the available studies are observational with limited capability to conduct experimental trials in pregnancy (Sammaritano et al., 2020). More knowledge about long-term outcomes of children born to mothers treated with biologics in pregnancy is still needed, and it is expected to grow with ongoing studies. In 2016, two sets of recommendations were issued guiding the use of conventional or biological DMARDs in pregnant females with rheumatic diseases with not much discrepancy between them except for addressing paternal use and specifying the timing for stoppage of some drugs before conception by the British Society of Rheumatology and British Health Professionals in Rheumatology (BSR-BHPR) guidelines (Flint et al., 2016; Götestam Skorpen et al., 2016; Wu and Ying, 2019). Updated recommendations were published early 2020 with more consistency and evidence for safety (Sammaritano et al., 2020).

In this article, we review the literature available concerning what is considered safe during pregnancy and lactation, what is not, and the future prospects.

GENERAL CONCEPTS

General Structure of Biologics

Currently, biologics employed for the treatment of SARD are either immunoglobulin G (IgG) full monoclonal antibodies (mAbs) or antibody fragments. IgG are generally characterized by high antigen affinity with less off-target activity (Strohl and Strohl, 2012). IgG1 is the most experimented and clinically used IgG subclass in biologics development, while very few types are constructed of other IgG isotypes (IgG2 and 4) (Ryman and Meibohm, 2017). The switch from chimeric to humanized to fully human antibodies improved the safety and tolerability of mAbs. Direct targets of mAbs are mostly inflammatory mediators such as tumor necrosis factor alpha (TNFα), interleukin 17 (IL-17), IL-6, IL-1, B-cell activating factor (BAFF), and less commonly cell markers (e.g., CD20) and cytokine receptors (e.g., IL-6R).

Although the functional part of the antibody is the antigen binding site, keeping the Fc portion intact preserves the molecule's long half-life. On the other hand, using antibody fragments enables better distribution and tissue penetration but with a shorter half-life and less functional affinity to the target molecule. As an alternative, adding an attachment to the antibody fragment such as polyethylene glycol (PEG) moiety prevents proteolysis, decreases renal clearance, and maintains a reasonable drug half-life (Schmid and Neri, 2019).

Maternal-Fetal Transport of Immunoglobulins

IgG and low levels of IgA are the only antibodies transferred from the mother to the fetus. Early in pregnancy, insignificant amounts of IgG are slowly transported by passive diffusion. Only 5–10% of the maternal level was measured at the end of the first trimester in blood samples obtained by cordocentesis (Jauniaux et al., 1995; Malek et al., 1996). A significant spike in maternal IgG transfer to the fetus starts at weeks 17–22 and increases thereafter resulting in higher, or at least similar, IgG levels in cord blood than maternal circulation at term, providing the newborn with a temporary passive immunity (Jauniaux et al., 1995; Malek et al., 1996; Saji et al., 1999; Simister, 2003; Lozano et al., 2018). The transfer is supported by placental structures such as neonatal Fc receptors (FcRn) as well as other placental Fcγ receptors (FcγR) (Wood et al., 1982).

At the maternal-fetal interface, FcRn are expressed on the placenta together with the three types of FcγR. However, it has been demonstrated that FcRn promotes the most IgG transport via a process of binding at the syncytiotrophoblast layer, endocytosis, and release into the fetal circulation (**Figure 1**) (Firan et al., 2001). IgG1 are preferentially transported, followed by IgG4, IgG3, and IgG2 (Leach et al., 1996; Simister et al., 1996; Kane and Acquah, 2009; Lozano et al., 2018). On the other side, FcRn on maternal endothelial cells and liver are responsible for maintaining IgG half-life including therapeutic mAbs via endosomal recycling and re-expression to the cell surface and unbinding (Junghans and Anderson, 1996; Pyzik et al., 2019).

Based on these concepts, whole mAbs with the Fc domains, particularly IgG1, will be transferred at high levels to the fetus through placental FcRn. Antibody formulations lacking the Fc portion or less readily transferable IgG subclass like IgG2, will keep the fetus relatively safe from the effects of the biologic therapy. The main concern about the transfer of bDMARD to the fetus is their theoretical potential to disrupt children`s immunity and response to infections and vaccinations.

BIOLOGICAL DRUGS USED IN RHEUMATOLOGY

TNFα Inhibitors

Currently, five anti-TNFα agents are being used in patients with various SARD, notably RA, SpA, and JIA among others (Monaco et al., 2015). They are the most studied in relation to pregnancy.

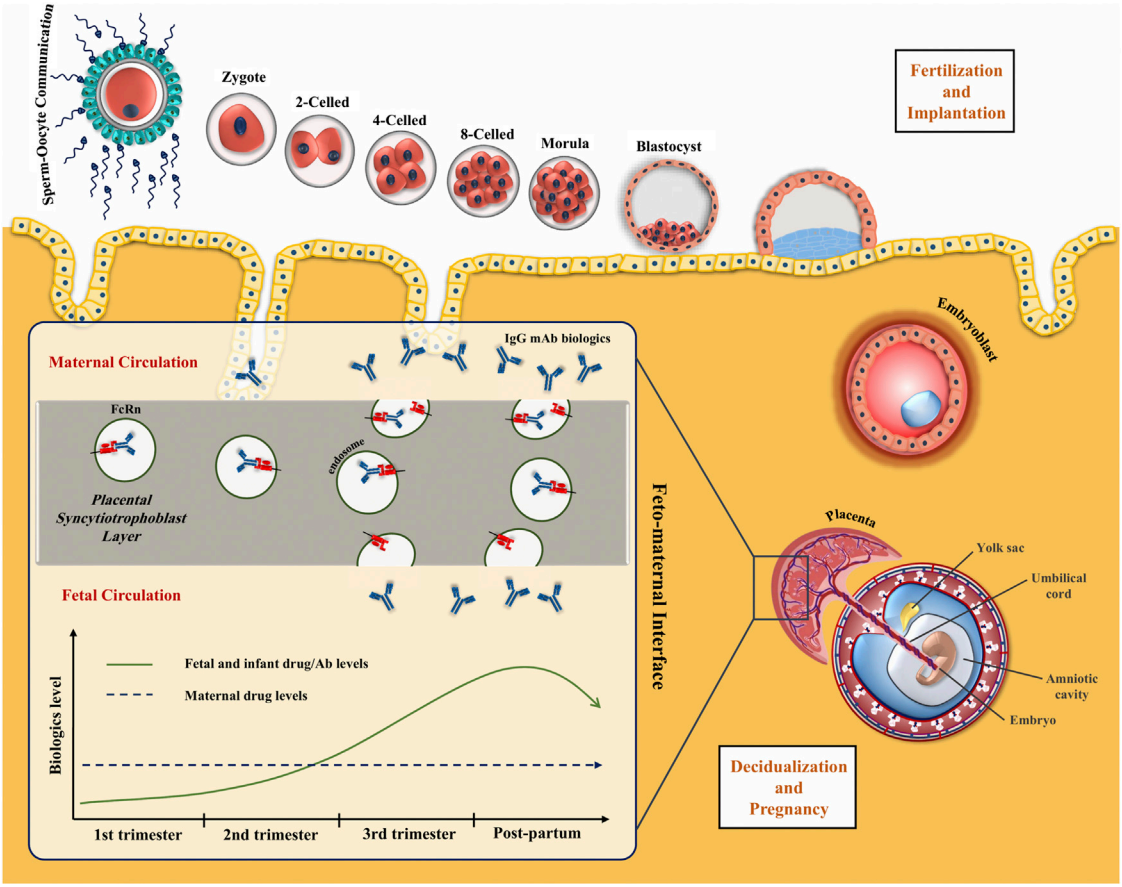


FIGURE 1 | Placental transfer of IgG mAbs. IgG is the only antibody class that crosses the placenta through the syncytiotrophoblast layer. FcRn internalizes the maternal IgG in the endosome and releases it on the other side of the syncytiotrophoblast layer. IgG transmission significantly increases during the third trimester of pregnancy.

Treatment with anti-TNFα drugs is usually accompanied by co-prescription of methotrexate (MTX), which should be stopped 1–3 months prior to attempting conception or when pregnancy is confirmed. Interestingly, anti-TNFα drugs were recently proposed as a potential treatment for refractory obstetric antiphospholipid syndrome (APS) (Alijotas-Reig et al., 2019).

Most of the data available about TNFα inhibitors, in particular infliximab, use in pregnancy are from studies on inflammatory bowel disease (IBD) patients. Observations from animal studies simulated to an extent what is being observed in humans. Despite transfer of anti-TNFα mAbs during organogenesis, no changes in fetal immune responses were reported. Safety with exposure throughout pregnancy and lactation was also ensured despite persistence of the drug up to 6 months in the blood of the exposed offspring (Treacy, 2000; Martin et al., 2007; Martin et al., 2008; Arsenescu et al., 2011).

Outcomes of Human Pregnancies with TNFα Inhibitors

The first retrospective analysis, from Centocor's infliximab safety database, included 96 pregnancies in women diagnosed mostly with RA and Crohn`s disease (CD) (94%) who were exposed early to infliximab. 67% of pregnancies resulted in a live birth, 14% spontaneous miscarriages, and 19% therapeutic miscarriages, which was comparable to pregnancy outcomes in CD without infliximab treatment (Katz et al., 2004). Similarly, Schnitzler et al. found that overall pregnancy outcomes, except for abortion, with infliximab and adalimumab treatment at conception or during pregnancy were not different from pregnancy outcomes before anti-TNFα therapy. The same was found for patients exposed for a long time before pregnancy, but the pregnancy outcomes were less favorable than those in pregnancies preceding IBD diagnosis (Schnitzler et al., 2011). Abortion rates were similar among all groups in this study; however, in another prospective study, the rate of miscarriages was higher in exposed mothers than in pre-conceptionally exposed or non-exposed women (Verstappen et al., 2011). Further data suggested that treatment with anti-TNFα drugs before or during pregnancy was not associated with poor global pregnancy outcomes based on the sum of obstetric and neonatal outcomes (Casanova et al., 2013). In addition, data from medical records concerning pregnant women exposed to immunosuppressive drugs included 56 womens with first trimester exposure to anti-TNFα who showed no significant increased risk in fetal adverse events or congenital malformations (Cooper et al., 2014). Similarly, outcomes after

infliximab exposure were not different from non-exposure outcomes as indicated by data derived from the TREAT registry of CD patients (Lichtenstein et al., 2018). A recent publication from the extensive Janssen's global safety surveillance database of infliximab exposed mothers revealed the outcomes of 1850 pregnancies. Spontaneous abortion, preterm labor, low birth weight rates were 12.1, 9.2, and 3.6% respectively, parallel to population rates. It provided valuable evidence for future recommendations about the continuation of infliximab late after the 30th week since they found no cumulative outcome difference between those exposed in the first and third trimesters (Geldhof et al., 2020).

Risk of Congenital Anomalies with Exposure to TNFα Inhibitors

TNFα has a role during embryo development; however, transfer of mAbs against TNFα at the beginning of organogenesis is trivial, leaving developmental impact unlikely.

Early observational data reported a reasonable safety profile. However, a causal relationship between TNFα inhibitors and the occurrence of VACTERL anomalies (V: vertebrae anomalies; A: anal anomalies; C: cardiac anomalies; T: tracheal problems; E: esophageal problems; R: renal defects; L: Limb defects) in a child born to a mother with psoriasis exposed to etanercept during pregnancy was reported (Carter et al., 2006). Consequently, scanning the FDA database from 1999 to 2005 of children born to mothers exposed to infliximab and etanercept revealed a surprisingly high number of congenital malformations, mostly cardiac with a high association of at least one of the anomalies of VACTREL group. However, when compared to a general population-based database of congenital anomalies (EUROCAT), there was no increase in VACTREL distribution among children exposed to TNFα blocker (Crijns et al., 2011).

A comparative prospective study of 492 pregnancies with SARD exposed mostly to adalimumab, infliximab, and etanercept at least in the first trimester and 1,532 non-exposed pregnancies revealed higher rates of major birth defects mostly cardiac anomalies even after adjustments to maternal differences. In addition, higher rates of preterm labor and low birth weights were reported in the exposed group. It was not clear whether these findings were related to drug exposure or insufficient disease control (Weber-Schoendorfer et al., 2015). Although not statistically significant, a higher risk was also reported in two other studies but with no increase in VACTERL incidence (Casanova et al., 2013; Bröms et al., 2016). Data of 154 womens from the OTIS registry found no increase in major or minor birth defects after *in-utero* exposure to adalimumab, including cases exposed throughout pregnancy (Burmester et al., 2017). Similar data were reported by a prospective study with exposure to infliximab, adalimumab, and etanercept (Diav-Citrin et al., 2014). The Janssen infliximab safety database has recently reported a 2% congenital anomaly rate which is not considered abnormal (Geldhof et al., 2020).

Although the etanercept structure preserves the Fc domain, lower deposition in the placenta and lower affinity to FcRn than infliximab and adalimumab were reported in *ex vivo* studies (Porter et al., 2016; Eliesen et al., 2020a). There was no evidence of poor pregnancy outcomes or major congenital anomalies in a large retrospective cohort from US health plan research database affiliated with Optum. The study had some limitations including the lack of data on the exact dose of the drug, timing, and total duration of administration (Carman et al., 2017).

A prospective Italian multi-center study endorsed the safety of anti-TNFα drugs given pre-conception or early in pregnancy for treating inflammatory arthritis (Bazzani et al., 2015). In addition, two consecutive meta-analyses in IBD patients found overall favorable pregnancy outcomes with no significant risk for miscarriages, preterm labor, low birth weight, or congenital anomalies (Narula et al., 2014; Shihab et al., 2016). Later, pooled data from a systematic literature review leading to the 2016 European League Against Rheumatism (EULAR) recommendations for use of antirheumatic drugs before and during pregnancy and lactation reported no increase in the frequency of miscarriages or congenital anomalies with the use of anti-TNFα during gestation (Götestam Skorpen et al., 2016).

The safety of certolizumab offers an alternative to rule out the uncertainties related to other anti-TNFα drugs. Unlike other drugs, an experimental study found no binding affinity between certolizumab and placental FcRn *in vitro*, clearly due to the absence of the Fc portion, and slight or no placental transfer of certolizumab in *ex vivo* model (Porter et al., 2016). In a case series of 13 womens with RA and SpA treated with certolizumab throughout pregnancy, the drug was not detected or detected at low levels in the cord blood (Förger et al., 2016). These results were in accordance with the previous study (Mahadevan et al., 2013). Using a highly sensitive assay for measuring certolizumab concentration, the CRIB study proved the lack of transfer of the drug from mothers exposed after the 30th gestational week to their children as the concentrations in cord blood were below measurement or trivial (Mariette et al., 2018).

International Guidelines

The EULAR recommendations considered the continuation of infliximab, adalimumab, and golimumab in the first part of pregnancy and certolizumab and etanercept till the end of pregnancy (Götestam Skorpen et al., 2016). In the same year, BSR-BHPR guidelines recommended safe continuation of infliximab till the 16th week, adalimumab and etanercept till the end of the second trimester, and certolizumab throughout pregnancy (Flint et al., 2016). The latest recommendations issued by the American College of Rheumatology (ACR) strongly considered the continuation of certolizumab at conception and during pregnancy. In the case of infliximab, golimumab, adalimumab, and etanercept, the ACR recommendations considered their continuation during first and second trimesters and discontinuation in the third trimester if the disease is well controlled. If the disease is active, the conditional continuation of these biological agents can be considered (Sammaritano et al., 2020).

Abatacept

Fewer safety data are available regarding biologics other than anti-TNFα. Abatacept is a recombinant selective fusion protein

that modulates a co-stimulatory signal T-cell activation (Blair and Deeks, 2017) and approved for the treatment of RA, JIA, and Psoriatic arthritis (PsA) (US Food and Drug Administration, 2017a).

Administration of high doses of abatacept to animal models during organogenesis was not associated with congenital malformations. Like other IgG mAbs, placental transfer of abatacept was described resulted in disturbances in the immune functions of juvenile rats (Kumar et al., 2015; Bristol-Myers Squibb, 2017). Lower drug levels are reported in foetal than in maternal serum and abatacept can be detected in breast milk (Pham et al., 2012; Saito et al., 2019b).

A combined retrospective/prospective analysis estimated spontaneous abortion rates in abatacept-exposed women as 25.8%, comparable to rates in the general population. Half of them were also exposed to methotrexate early in pregnancy and the rate of congenital anomalies was increased in comparison with that reported in the general population (8.1% vs. 3–5%) (Kumar et al., 2015). Limitation of records about disease activity during pregnancy and comorbidities make such data less reliable. Current guidelines recommend stoppage of abatacept at conception and during pregnancy (Flint et al., 2016; Götestam Skorpen et al., 2016; Sammaritano et al., 2020). A running registry for pregnancies under abatacept treatment is still collecting additional safety data (Bristol-Myers Squibb, 2019).

Tocilizumab

Tocilizumab is another recombinant humanized IgG1 mAb that targets the receptors of the pleiotropic cytokine IL-6 (Nishimoto and Kishimoto, 2008). It is indicated for the treatment of RA unresponsive to DMARDs and/or anti-TNFα therapy, polyarticular and systemic JIA, and giant cell arteritis (US Food and Drug Administration, 2019b).

Tocilizumab safety was supported by animal studies showing normal fetal development, average postnatal development and satisfactory immunoglobulin production (Sakurai et al., 2012). Placental transfer and cord levels of tocilizumab are lower than those of anti-TNFα IgG1 and natural IgG (Saito et al., 2019a; Tada et al., 2019; Moriyama et al., 2020).

Outcomes of prospectively and retrospectively followed pregnancies from Roche safety database were published in 2016. Most of the patients were exposed pre-conceptionally or in the first trimester with only 17 patients being exposed during the second and third trimesters. Compared to population rates, higher incidence of preterm labor and low birth weight was reported although the limited data about disease activity after tocilizumab suspension hindered the explanation of the cause of these high rates. There was no increase in congenital birth defects. Despite the insufficient number of cases, pregnancies with exposure beyond the first trimester had very good outcomes (Hoeltzenbein et al., 2016). Conflicting results were published about rates of spontaneous abortions related to tocilizumab. While this database and a case series reported a high percentage of spontaneous abortions (Hoeltzenbein et al., 2016; Weber-Schoendorfer and Schaefer, 2016), data from a smaller Japanese safety study did not find an increase in abortion rates or birth defects (Nakajima et al., 2016). It is recommended, by the EULAR, BSR-BHPR and ACR guidelines, that tocilizumab should be stopped prior to conception and during pregnancy though harm to the fetus is unlikely with unintentional exposure.

Anti-B Cell Therapies (Rituximab, Belimumab)

Rituximab is a chimeric anti-CD20 mAb approved for the treatment of anti-TNFα non-responsive RA, Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) (US Food and Drug Administration, 2012) and is used off-label in some situations such as refractory immune thrombocytopenia and lupus nephritis. Rituximab represents an attractive option to abort severe disease flares in pregnancy especially in SLE and for maintaining remission if received before conception since it continues to have a B cell modulating effect for a long duration beyond its half-life (approximately 110 days) (Breedveld et al., 2007). Giving rituximab to monkeys during organogenesis resulted in low B-cell count in their newborns. It was also shown to cross the placenta like other IgG mAbs and it was previously categorized as category C (US Food and Drug Administration, 2012).

Human pregnancy data about its safety are scanty. In a systematic review by Das et al., including studies on different diseases treated with rituximab around conception, rates of abortions and preterm labor were 12% and 47%, respectively. However, considering the retrospective nature of the studies included in that review, it is difficult to evaluate for confounding factors such as other medications, comorbidities, and disease activity status (Das et al., 2018).

Even when rituximab was administered near conception with persistence of maternal drug levels for weeks after the last infusion, most of the neonates born to mothers treated with rituximab had no congenital anomalies explained by minimal IgG transfer early during organogenesis (Thurlings et al., 2010; Das et al., 2018). Rituximab was considered only for emergency use in life threatening SLE disease activity during pregnancy and should be stopped at pre-conception (Götestam Skorpen et al., 2016; Sammaritano et al., 2020). The BSR-BHPR recommendations specified that rituximab should be stopped 6 months pre-conception (Flint et al., 2016).

Another anti-B cell therapy, belimumab, which is a fully human IgG1 mAb directed against the soluble form of the BAFF was approved by the FDA in 2011 for use in adult autoantibody-positive moderately active SLE (US Food and Drug Administration, 2019c).

Belimumab intravenously administered throughout pregnancy in animal studies was well tolerated by mothers and fetuses with no noticeable immunological or developmental adverse events except for a low B-cell population, which is expected (US Food and Drug Administration, 2019c). Although cumulative reports show some births with congenital anomalies, the data are insufficient to relate their occurrence to belimumab (Danve et al., 2014; Kumthekar et al., 2017; GlaxoSmithKline, 2020).

A registry is kept by GlaxoSmithKline to evaluate pregnancies and children born under belimumab exposure (GlaxoSmithKline,

2020). It would be important to confirm that anti-B cell therapy is a safe treatment option for SLE in pregnancy and breastfeeding since the disease has a serious potential for flaring up during pregnancy and postpartum period.

Recently, the ACR recommendations conditionally allowed the continuation of belimumab during conception which is a step forward from the earlier EULAR and BSR-BHPR recommendations that considered stopping it before conception. However, both still recommend against its continuation once pregnancy is confirmed (Flint et al., 2016; Götestam Skorpen et al., 2016; Sammaritano et al., 2020).

IL-17 Inhibitors

Secukinumab followed by ixekizumab were the two FDA-approved IL-17 inhibitors for the treatment of moderate-to-severe plaque psoriasis, psoriathic arthritis (PsA), and ankylosing spondylitis (AS). They interfere with the pro-inflammatory activity of IL-17 which has been recently considered a key pathogenic player (Koenders and van den Berg, 2016; Chandran et al., 2020; Genovese et al., 2020). Secukinumab is a recombinant human monoclonal IgG1/κ antibody while ixekizumab is a humanized IgG4 mAb. Both can block the IL-17/IL-17R interaction through selective IL-17A neutralization (Frieder et al., 2018). Like other IgG molecules, secukinumab transfer starts after the 17th week and moreover throughout pregnancy (Saji et al., 1999; Simister, 2003).

Whereas nearly all clinical trials consider gestation as exclusion criteria, pregnancy outcomes using these monoclonal antibodies is remains uncertain. According to Novartis global safety database about outcomes of pregnancies mostly exposed to secukinumab at conception before stopping the drug in pregnancy, secukinumab was not related to abnormal rates of miscarriage or congenital abnormalities among the 292 study participants (238 maternal exposure) (Porter et al., 2017; Warren et al., 2018; Puchner et al., 2019). There are no accessible data about exposure throughout pregnancy. Accordingly, it is still recommended against its use in pregnancy by the European Medicines Agency (Warren et al., 2018; European Medicines Agency, 2019).

Studies on animal models found no embryo-fetal toxicity or teratogenic effects of secukinumab or ixekizumab although an increase in neonatal losses was reported in monkeys after exposure to ixekizumab at the 20th week of gestation (Clarke et al., 2015; Novartis Pharmaceuticals Corp, 2020). Of the two IL-17 inhibitors, secukinumab was mentioned only in the relevant ACR guidelines that recommended its discontinuation before conception and during pregnancy (Sammaritano et al., 2020).

IL-12/IL-23 Pathway Blocker

Ustekinumab is a human IgG1/κ monoclonal antibody that blocks the p40 subunit of IL-12 and IL-23 cytokines (Benson et al., 2011). Ustekinumab has been introduced as an FDA approved bDMARD in the treatment of moderate to severe plaque psoriasis, active PsA, and IBD (US Food and Drug Administration, 2019a). Animal studies have reported no adverse effects on neonatal development during ustekinumab administration (Lund and Thomsen, 2017; US Food and Drug Administration, 2019a). Up to 2017, a total of 12 pregnancies in which ustekinumab was used has been reported by Venturin et al. Two out of 12 pregnancies have been aborted in the second and eighth weeks. However, the rest of the pregnancies were delivered uneventfully, and the babies were born without any anomalies (Venturin et al., 2017). According to a report on seven patients with psoriasis who were under ustekinumab treatment, 10 pregnancies resulted in eight healthy infants with no malformation (Watson et al., 2019). Maternal-fetal transfer of ustekinumab is assumed to be similar to other IgG1 mAbs. However, no new safety information was recorded by the most recent clinical reports. Therefore, they recommended that the final application be discontinued 8–12 weeks prior to parturition (Gisbert and Chaparro, 2020). According to both the EULAR and ACR statements, ustekinumab should be stopped before attempting conception and during pregnancy (Götestam Skorpen et al., 2016; Sammaritano et al., 2020).

IL-1 Inhibitors

Inhibitors of IL-1 have been recently employed in the treatment of systemic autoinflammatory syndromes. Experience with therapeutic agents like anakinra, canakinumab, and rilonacept is limited. Anakinra is a recombinant protein that blocks IL1 receptor. Canakinumab is a full mAb while rilonacept is a fusion protein including the IL-1 binding motifs of IL-1 receptors coupled to the Fc domain of human IgG1. Few publications exist regarding their safety in gestation. Anakinra and canakinumab were well tolerated and pregnancy outcomes in small studies were satisfactory including cases of paternal and late pregnancy exposures (Chang et al., 2014; Youngstein et al., 2017; Venhoff et al., 2018).

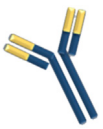
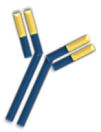
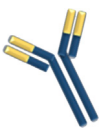
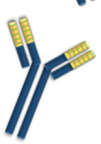
It is noteworthy that oligohydramnios was previously reported, and renal agenesis was observed in two of anakinra exposed children which is worrisome considering the small number of the published cases (Chang et al., 2014; Youngstein et al., 2017). For the time being, anakinra seems to be safer to be prescribed in pregnancy than canakinumab with more evidence published and shorter half-life (Youngstein et al., 2017). The official recommendations still indicate that anakinra should be stopped before conception (Flint et al., 2016; Götestam Skorpen et al., 2016; Sammaritano et al., 2020).

Rilonacept studies in humans are lacking but animal pregnancy studies have raised concern about a relation between the drug and skeletal anomalies and fetal deaths (US Food and Drug Administration, 2008).

Eculizumab

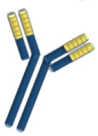
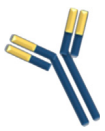
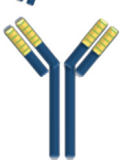
Eculizumab, the humanized anti-C5a antibody, was engineered as a unique IgG2/4κ formulation with weakened Fc functionality that limits its passage through the placental barrier and therefore theoretically renders it safer in pregnancy than other biologics (Hashira et al., 2000; Lozano et al., 2018; Sarno et al., 2019). It strongly binds C5 and interferes with its cleavage to the pro-inflammatory C5a and the terminal complement member C5b-9 (Schatz-Jakobsen et al., 2016). Eculizumab is approved by FDA in the treatment of atypical hemolytic uremic syndrome (aHUS), paroxysmal nocturnal hemoglobinuria (PNH), and generalized Myasthenia Gravis (gMG) (US Food and Drug Administration, 2017b).

TABLE 1 | Common Biological Drugs in SARDs and their indications.

Biologic name (Trade name)	Target	Type (Schmid and Neri (2019))	IgG subclass	Structure	Risk category FDA	Risk category TGA (Ngian et al. (2016))	FDA approved indication	Common off label and investigatory indications in rheumatology
Infliximab (remicade)		Chimeric mAb	IgG1		B	C	-AS -RA -Pediatric and adult CD and UC -PsA and plaque Psoriasis	BD Hatemi et al. (2018) Sarcoidosis Loza et al. (2011). Refractory OAPS Alijotas-Reig et al. (2019) Pyoderma gangrenosum. Maverakis et al. (2020)
Adalimumab (humira)	TNFα	Fully human mAb	IgG1		B	C	-As -RA -JIA -Pediatric and adult CD and UC -PsA and plaque psoriasis -Uveitis	
Golimumab (simponi)		Fully human mAb	IgG1		B	C	-As -PsA -RA - UC	
Etanercept (enbrel)		Recombinant TNFα receptor added to Fcγ	IgG1		B	B2	-As -RA -Polyarticular JIA -PsA and plaque psoriasis	
Certolizumab (cimzia)		Humanized fab fragment and PEG	—		B	C	-RA -As -Non-radiographic axial SpA -CD -PsA	
Abatacept (orencia)	CD80 CD86	Extracellular region of CTLA-4 added to Fcγ	IgG1		C	C	-RA -JIA	RA-ILD Fernández-Díaz et al. (2020)
Rituximab (rituxan)	CD20	Chimeric mAb	IgG1		C	C	-RA	Refractory LN Stolyar et al. (2020) Refractory NPSLE Pamfil et al. (2015) Refractory IHA and thrombocytopenia Fanouriakis et al. (2019) ANCA associated vasculitis Yates et al. (2016) DM Oddis et al. (2013) SS Ramos-Casals et al. (2020) RA-ILD Dai et al. (2020) IgG4-RD Brito-Zerón et al. (2016)
Belimumab (benlysta)	BAFF	Fully human mAb	IgG1		C	C	-Active, autoantibody positive SLE	Add-on therapy in LN Ward and Tektonidou (2020)
Secukinumab (cosentyx)		Humanized mAb	IgG1		B	C	-As -PsA and plaque psoriasis	NA

(Continued on following page)

TABLE 1 | (*Continued*) Common Biological Drugs in SARDs and their indications.

Biologic name (Trade name)	Target	Type (Schmid and Neri (2019))	IgG subclass	Structure	Risk category FDA	Risk category TGA (Ngian et al. (2016))	FDA approved indication	Common off label and investigatory indications in rheumatology
Ixekizumab (taltz)	IL-17	Fully human mAb	IgG4		NA	C	-As -PsA and plaque psoriasis	NA
Ustekinumab (stelara)	IL-12/ IL-23	Fully human mAb	IgG1		B	B1	-PsA -CD and UC	NA
Tocilizumab (actemra)	C5	Humanized mAb	IgG1		C	C	-RA -GCA -Polyarticular and systemic JIA CRS	Castleman's disease PMR Uveitis Rubbert-Roth et al. (2018)
Anakinra (kineret)	IL-1R	Recombinant non-glycosylated protein	—		B	B1	-RA -CAPS	AOSD BD FMF Systemic JIA
Canakinumab (ILARIS)	IL-1	Fully human mAb	IgG1		C	D/X	-FCAS -MWS	RA Vitale et al. (2016) Gout So et al. (2018)
Rilonacept (arcalyst)	IL1	IL-1R binding motifs coupled to the Fc domain	IgG1		C	NA	-CAPS -FCAS -MWS	Gout So et al. (2018)
Eculizumab (soliris)	IL-6	Humanized mAb	IgG2/4		C	B2	-aHUS -gMG -PNH	HELLP C-APS Stefanovic (2019)
Denosumab (prolia/Xgeva)	RANKL	Fully human mAb	IgG2		D	NA	Postmeno-pausal osteoporosis	PLO Sánchez et al. (2016)

NA, no available data; ACR, american college of rheumatology; aHUS, atypical hemolytic uremic syndrome; ANCA, anti-neutrophil cytoplasmic antibodies; AOSD, adult onset still's disease; AS, ankylosing spondylitis; BAFF, B-cell activating factor; BD, behcet's disease; C, complement; C-APS, catastrophic antiphospholipid syndrome; CAPS, cryopyrin-associated periodic syndromes; CD, crohn's disease; CRS, cytokine release syndrome; DM, dermatomyositis; EULAR, european league against rheumatism; Fab, fragment antigen-binding; Fc, fragment crystallizable; FCAS, familial cold autoinflammatory syndrome; FDA, US food and drug administration; FMF, familial mediterranean fever; GCA, giant cell arteritis; gMG, generalized myasthenia gravis; IgG, immunoglobulin G; IHA, immune hemolytic anemia; IL, interleukin; ILD, interstitial lung disease; IgG4-RD, immunoglobutlin G4 related disease; JIA, juvenile idiopathic arthritis; LN, lupus nephritis; mAb, monoclonal antibody; MWS, muckle-wells syndrome; NPSLE, neuropsychiatric systemic lupus erythematosus; OAPS, obstetric anti-phospholipid syndrome; PEG, poly-ethylene glycol; PMR, poly-myalgia rheumatica; PNH, paroxysmal nocturnal hemoglobinuria; PLO, pregnancy and lactation associated osteoporosis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RANKL, receptor activator of nuclear factor kappa-B ligand; SARD, systemic autoimmune rheumatic diseases; SS, sjögren syndrome; TGA, therapeutic goods administration; TNFα, tumor necrosis factor α; UC, ulcerative colitis.

It has also been shown to give good responses in refractory cases of catastrophic antiphospholipid syndrome (C-APS) and Hemolysis, Elevated Liver enzyme, and Low Platelet levels (HELLP) syndrome (Stefanovic, 2019). These all are serious conditions induced by complement activation that can be triggered by pregnancy, making the therapeutic use of eculizumab a possibility to be strongly considered. In the current literature, outcomes of only two triple antibody-positive APS patients treated with eculizumab during pregnancy were reported. Secondary thrombotic microangiopathy also complicated pregnancy in one of them. The two patients received eculizumab in the third trimester and delivered, prematurely by cesarean sections, healthy newborns (Gustavsen et al., 2017; Rovere-Querini et al., 2018).

TABLE 2 | Risk categorization by FDA and TGA for use of drugs in pregnancy.

Category	FDA	TGA
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.	B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage. B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage. B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.
D	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Eculizumab was either not detected or detected at low ineffective titers in cord blood after administration in pregnancy including cases when mothers received it in late weeks. That is partially explained by its unique formulation and not by the strong binding between eculizumab and FcRn observed in*in vitro* studies. Poor pregnancy events were documented in some cases but attribution to the severity of the underlying condition as PNH or aHUS is more likely than to eculizumab itself (Kelly et al., 2010; Hallstensen et al., 2015; Miyasaka et al., 2016; Servais et al., 2016; Sarno et al., 2019). Eculizumab safety for use in pregnancy has not yet been addressed by the current rheumatology guidelines.

Denosumab

Denosumab is a fully human IgG2 which is the least IgG subclass to be transferred through the feto-maternal interface. Its use for the treatment of pregnancy and lactation-associated osteoporosis, which is a relatively underreported condition with no identifiable treatment consensus, was addressed in some case reports with good results (Sánchez et al., 2016; Ijuin et al., 2017). However, it is contraindicated in pregnancy and lactation following discouraging animal studies which showed high still-birth and newborn mortality rates (Bussiere et al., 2013; Okamatsu et al., 2017).

A summary of the characteristics of the common drugs used in SARD including the risk category according to Food and Drug Administration (FDA) and Therapeutics Good Administration (TGA) is reported in **Tables 1, 2**.

BIOLOGIC DRUG-INDUCED MATERNAL AND INFANT IMMUNOLOGICAL CHANGES

Complex immunological changes naturally occur in pregnancy. Pregnant women are generally considered immunocompromized with more susceptibility to various infections (Mor and Cardenas, 2010). Administration of biological drugs surely induces additional variations in the maternal immune responses.

An insufficiently studied aspect is how much the drug level and efficacy are affected by pregnancy status. By measuring maternal infliximab and adalimumab levels each trimester in 25 pregnancies with IBD, an increase in infliximab with the

progress of pregnancy was unexpectedly found. Adalimumab showed steady drug levels, although infliximab was discontinued earlier than adalimumab (Seow et al., 2017). Such findings were considered as a possible explanation for the higher cord blood levels of infliximab, which inversely correlated with the interval between the last dose and birth date, and the more delayed infliximab clearance from infant blood in former studies (Mahadevan et al., 2013; Julsgaard et al., 2016). Therefore, the authors concluded that monitoring anti-TNFα drug level, particularly in the second trimester, may offer a guide for third trimester dosing to ensure safety of the baby and protection to the mother from intrapartum or postpartum disease activity.

The 2014 meta-analysis by Narula et al. concluded that the benefit from anti-TNFα therapy overweighs any possible poor outcomes to the fetus or the mother (Narula et al., 2014). However, as their use is becoming more common, there are reports of a higher incidence of maternal infections that might be related to the use of anti-TNFα treatment in pregnancy. A study reported the records of twenty-five children exposed during gestation to infliximab/adalimumab; 80% of them were also breastfed till the median age of 6 months. Seven children had a mild decrease in immunoglobulin levels (IgA and IgG) without relevant clinical signs, while lymphocytic subpopulation counts were normal. Infections, mostly mild upper respiratory tract infections, were recorded in 80% of the babies. However, the reported infections do not seem to be therapy-related since they occurred late after the drug clearance (Bortlik et al., 2014). In the case series of women treated with certolizumab throughout pregnancy, maternal infections developed in three out of 13 included women; however, two of them were on concomitant low dose steroid therapy (Förger et al., 2016). A large cohort of French IBD patients was retrospectively investigated; 1,457 anti-TNFα (mostly infliximab and adalimumab) exposed patients were compared with 9,818 non exposed patients. Maternal infection rate in the first group was significantly higher than in non-exposed patients (Luu et al., 2018).

Another example of confusing maternal responses to biologic therapy during pregnancy is the need to increase doses and frequencies of eculizumab and increase the need for red blood cell transfusions in a subset of pregnant patients with PNH which might be explained by increased lysosomal metabolism of eculizumab and physiologic dilutional pregnancy changes (Kelly et al., 2015). Following treatment of a pregnant APS patient with eculizumab infusions, complement regained normal activity soon after infusions earlier than expected (Gustavsen et al., 2017). For the infant, the cord blood levels of various biologic drugs at birth display different values. Cord blood levels were high for infliximab and adalimumab (≈2.6 and 1.5% fetal to maternal ratio, respectively) (Mahadevan et al., 2013; Kanis et al., 2018), and not detected or negligible in the case of certolizumab, etanercept, and eculizumab (Murashima et al., 2009; Mariette et al., 2018). Most drugs with high levels at birth persisted in fetal blood for 4–9 months (Julsgaard et al., 2016).

Reversible change in immune cell counts is a well-recognized side effect particularly with the anti B-cell therapy. Neutropenia with serious skin infections was reported after treatment with infliximab in some reports (Guiddir et al., 2014). Apparently harmless reversible low infant total and B cell lymphocyte count without a significant rise in infection rates or abnormal vaccination course was reported after exposure to rituximab (Azim et al., 2010; Chakravarty et al., 2011; Das et al., 2018). A similar effect was seen in one case report with belimumab exposure (Bitter et al., 2018). These cellular effects were mostly transient and reverted to normal within months. Following eculizumab exposure, assessment of infant complement revealed normal activity (Hallstensen et al., 2015).

Since patients on anti-TNFα therapy display more susceptibility to mycobacterial infections due to interference with the IL-12/IFN-γ pathway, this pathway was investigated in newborns exposed to infliximab/adalimumab throughout pregnancy. Seven exposed and eight non-exposed children were followed for 12 months. Apart from one child who had recurrent infections after the 6th month of age, all showed no increase in infection rates with good developmental milestones. Leucocyte and lymphocyte counts were normal. T-regulatory cell values were lower than average in exposed children and defects in IL-12/IFN-γ pathway led to subnormal response to mycobacterial challenge. B-cell development and maturity are also thought to be affected by TNFα inhibition. Although this study showed that the B-cell population was shifted more to the naïve cells in exposed children, immunoglobulin levels were normal and antibody responses to diphtheria, tetanus, and pneumococcal vaccines were average (Esteve-Solé et al., 2017).

BREASTFEEDING

The risk of transfer of biologics in breast milk is generally lower than that of placental transfer. Unlike IgA, overall secretion of IgG is scarce in breast milk. The preferential secretion of IgG subclasses is different from the placental one in which IgG3 and IgG4 are secreted more than IgG1 (Gasparoni et al., 1992). Transfer of the Fab fragment is even much lower than full IgG (Nesbitt et al., 2006). Moreover, mAb oral bioavailability is limited due to their large molecular size and the fact that degradation by proteolytic enzymes (Zelikin et al., 2016; Ryman and Meibohm, 2017). Nevertheless, FcRn are expressed at the intestinal mucosal surface of the newborn and can mediate the transfer of antibodies which escape proteolysis (Clowse et al., 2017; Pyzik et al., 2019).

Following these concepts, breast milk levels of almost all anti-TNFα and other mAb biologics are either very low or undetectable and mostly not be delivered to the nursing child's circulation (Murashima et al., 2009; Ben-Horin et al., 2011; Clowse et al., 2017; Matro et al., 2018). Nevertheless, the reassurance of physicians for the use in clinical practice needs more studies reporting actual outcomes with breastfeeding.

The best evidence available is for certolizumab. It was not detected in the breast milk of nursing mothers following treatment with certolizumab (Mahadevan et al., 2013; Förger et al., 2016). A post-marketing multicenter study confirmed minimal or no excretion of certolizumab or PEG in breast milk and negligible relative infant dose of certolizumab (Clowse et al., 2017). In parallel, insignificant amounts of etanercept

TABLE 3 | Guidelines for continuation of biological drugs in pregnancy, lactation and male partners.

Biologic name	Outcomes of pregnancy animal studies[a]	ACR	EULAR	BSR/BHPR
		Pregnancy/Breastfeeding/Paternal Sammaritano et al. (2020)	Pregnancy/Breastfeeding/Paternal Götestam Skorpen et al. (2016)	Pregnancy/Breastfeeding/Paternal Flint et al. (2016)
Infliximab	Infliximab analogue did not result in fetal malformations or developmental effects in mice offspring.	Conditional[b]/Continue/Continue	Stop at week 20/Continue/-	Stop at week 16/Continue/Continue
Adalimumab	Exposing cynomolgus monkeys to doses higher than the MHRD did not result in fetal malformations or harms.		Stop at week 20/Continue/-	Conditional[b]/Continue/Continue
Golimumab	No neonatal or postnatal developmental harm with pregnancy and breastfeeding in monkeys.		Conditional[b]/NA/-	NA/NA/NA
Etanercept	No evidence of mal-formations in rats and rabbits exposed to etanercept during embryogenesis. Normal post-natal development of rats exposed to doses 48 times the human dose.		Continue/Continue/-	Conditional[b]/Continue/Continue
Certolizumab	Studies in rats using antimurine analogue resulted in no fetal harms or malformations	Continue/Continue/Continue	Continue/Continue/-	Continue/Continue/Continue
Abatacept	In-utero and juvenile exposure of rats to doses 11 times the MHRD resulted in disturbance in fetal immune response.	Discontinue/Conditional/NA	Discontinue[c]/Discontinue[c]/-	Discontinue/NA/NA
Rituximab	Animal exposure showed no teratogenic effect but decrease in B-cell lymphoid tissue and reversible decline in B-cell population.	Conditional[d]/Conditional[d]/Continue	Discontinue[c]/Discontinue[c]/-	Discontinue 6 mths pre-conception/NA/Continue
Belimumab	Exposure of monkeys throughout pregnancies to high doses resulted in no fetal malformations. Fetal decrease in peripheral and lymphoid tissue B-cell population, increase in total IgG and decrease in IgM were reported. All changes recovered within the first year of life.	Discontinue/Conditional[e]/NA	Discontinue[c]/Discontinue[c]/-	Discontinue/NA/NA
Secukinumab	No fetal toxicity or malformations on exposure to high doses. Secukinumab analogue did not lead to abnormal morphological or immunological effects In a pre- and post-natal developmental study.	Discontinue/Conditional[e]/NA	—	—
Ixekizumab	No fetal toxicity or malformations was observed on exposure to high doses In pre and post-natal developmental studies, no abnormal morphological or immunological effects. However, early neonatal deaths were reported, unlikely due to ixekizumab.	—	—	—
Ustekinumab	In embryofetal and developmental studies, exposure >100 times higher than the human SC exposure resulted in no fetal toxicities, malformations, developmental, morphological or immunological effects. Unexplained 2 neonatal deaths were reported.	Discontinue/Conditional[e]/NA	Discontinue[c]/Discontinue[c]/-	—
Tocilizumab	No fetal toxicity, malformations, developmental or immunological abnormalities were reported. Increase in rate of abortions was reported in monkeys at doses 1.25 higher than the MRHD.	Discontinue/Conditional[e]/NA	Discontinue[c]/Discontinue[c]/-	Discontinue 3 mths pre-conception/NA/NA
Anakinra	Studies on rabbits and mice at doses 25 times the MRHD resulted in no fetal harm.	Discontinue/Conditional[e]/Conditional	Discontinue[c]/Discontinue[c]/-	Discontinue/NA/NA
Canakinumab	Studies on monkeys at doses 11 times the MRHD showed no malformations. Rate of skeletal developmental delay due to incomplete ossification was increased.	—	—	—
Rilonacept	Study on monkeys reported rib and vertebral abnormalities. There was also increase in rate of stillbirths and neonatal deaths.	—	—	—

(Continued on following page)

TABLE 3 | (*Continued*) Guidelines for continuation of biological drugs in pregnancy, lactation and male partners.

Biologic name	Outcomes of pregnancy animal studies[a]	ACR	EULAR	BSR/BHPR
		Pregnancy/Breastfeeding/ Paternal Sammaritano et al. (2020)	Pregnancy/Breastfeeding/ Paternal Götestam Skorpen et al. (2016)	Pregnancy/ Breastfeeding/Paternal Flint et al. (2016)
Eculizumab	Exposure of mice to doses up to 8 times the MRHD early in pregnancy resulted in no abnormality. Exposure during organogenesis resulted in 2/230 neonates with retinal dysplasia. Exposure from implantation to weaning was associated with higher death rate among pups. All live births showed normal development.	—	—	—
Denosumab	In monkeys, high still-birth and newborn mortality rates due to intrinsic fetal defects such as increased bone mass, insufficient hematopoiesis, hypoglycemia, and hypocalcemia. Abnormal bone growth with decreased strength, absence of lymph-node groups, dental dysplasia and reduced neonatal growth were reported in the offspring.	—	—	—

[a]*Animal experimental data were extracted from FDA labes of each drug.*
[b]*Stop before third trimester.*
[c]*Discontinue except if no pregnancy compatible alternative to control activity.*
[d]*Consider use in organ/life threatening conditions.*
[e]*Limited available data but expected minimal transfer in breast milk.*
NA: No available recommendation due to limited published data. — Not mentioned in the guidelines. MHRD, maximum human recommended dose.

were detected in breast milk following treatment during breastfeeding and the drug was not detected in infant circulation (Murashima et al., 2009; Berthelsen et al., 2010; Keeling and Wolbink, 2010). Breast milk levels of other TNFα blockers and rituximab follow the same pattern as etanercept with low levels excreted in breast milk (Matro et al., 2018). The 2020 ACR guidelines considered all the TNFα inhibitors and rituximab compatible with breastfeeding with a strong recommendation although based on a low level of evidence. No data were available to support recommendations for its use during lactation by the EULAR and the BSR-BHPR guidelines. It is advised against nursing for 6 months after exposure to rituximab by FDA (US Food and Drug Administration, 2018).

There are no or very few data regarding other IgG1 mAbs (belimumab, tocilizumab, secukinumab, ustekinumab) and anakinra. They are conditionally recommended for use in pregnancy putting into consideration patient benefits vs. risks to the child (Sammaritano et al., 2020). Breast milk levels of belimumab were recently reported to be low at 1/200 to 1/500 of maternal values (Saito et al., 2020). Anakinra is profusely excreted in breast milk but infant drug levels have not yet been clearly measured. Since IL1 receptor antagonists are naturally present in breast milk, it was presumed that anakinra would not have a detrimental effect on the infant. That was confirmed by several studies that showed average developmental progress in children breastfed by mothers receiving anakinra (Chang et al., 2014; Youngstein et al., 2017; Smith and Chambers, 2018). Similarly, the IgG2/4κ eculizumab was not detected in breast milk samples and no developmental problems were published (Kelly et al., 2015; Miyasaka et al., 2016).

Table 3 summarizes the guidelines for using biological drugs during pregnancy, lactation, and for male partners according to ACR, BSR/BHPR and EULAR committees.

The data from animal studies are also summarized in **Table 3**.

VACCINE RESPONSES AND LONG-TERM OUTCOMES

More informative long-term data regarding outcomes of children after exposure to biological drugs *in-utero* or during nursing are needed. In addition, precise assessment of responses to vaccines, especially for the first-year doses, is definitely needed to ensure successful immunization after inactivated vaccines and exclude the risk of serious side effects with live-attenuated vaccines. Anticipated persistence of mAb biologics in infant blood and B-lymphocyte depletion following exposure to anti B-cell therapy requires more research to determine the time of clearance of different biologics and proper planning of an effective and safe vaccination schedule. Reports about responses to inactivated vaccines are more available than live-attenuated since it is a common practice to delay live-attenuated vaccines till after the first year.

Although data from drug registries and observational studies report minimal or no side effects in infants exposed to infliximab *in-utero*, early reports revealed a serious disarray in infants` immune responses to Bacille Calmette–Guérin (BCG) vaccines (Cheent et al., 2010).

A study showed that, postnatally, infliximab was cleared from infant blood over a longer duration than adalimumab (mean 7.3 vs. 4 months), raising concerns about infant`s response to live-

attenuated vaccines, particularly BCG, which is still obligatory in many countries (Julsgaard et al., 2016). In this study, authors found that 4/80 (5%) of infants suffered bacterial infections and 16/80 (20%) had viral infections, but most of them were exposed to anti-TNFα *in-utero* and also to thiopurines.

During a 2-years follow-up period, 34 children exposed *in-utero* to anti-TNFα agents (8 after the first trimester) showed no difference in growth and developmental parameters nor in the incidence of congenital malformations in comparison to controls. Post-vaccination responses and adverse events were also similar except for one etanercept exposed child who contracted chickenpox infection after insufficient response to the relevant vaccine (Dall'ara et al., 2016). The World Congress of Gastroenterology statements in 2011 recommended giving special attention to the timing of biological therapy during pregnancy and postponing delivery of live-attenuated vaccines to exposed children until the drug is no longer detected in their circulation (Mahadevan et al., 2011).

According to Bortlik et al., serologic antibody responses to first year scheduled inactivated vaccines were found satisfactory except for *Hemophilus influenza* B (HiB) vaccine which produced below threshold protective antibody levels in 6/15 examined children (Bortlik et al., 2014). In a recent evaluation of the long-term impact of *in-utero* exposure to anti-TNFα therapy, Duricova et al. followed 72 exposed children older than 12 months of age and compared them with 69 non-exposed children for a duration of follow up that ranged from 3 to 4 years. Most of the mothers had CD and were treated with infliximab, which was used until 17–30 weeks of gestation. There was no significant variation between groups of children regarding growth, psychomotor development, allergy status, and infection rate during the first year of life and the period of follow-up (Duricova et al., 2019). Vaccines caused more adverse events in the exposed group, but that difference was not statistically significant, and none of the adverse events was critical (23 vs. 11.6% $p = 0.06$). Of the children who received scheduled vaccines, serologic response was adequate in >95% of exposed children except for HiB and mumps vaccines, for which fewer children in exposed and control groups had an adequate serologic response (65.3 vs 12.5%) and (75.7 vs. 81.3%) of tested children (Duricova et al., 2019). In another study, children exposed to biologics (including anti-TNFα and ustekinumab) during breastfeeding in the first year of life showed average developmental milestones and infection rates similar to controls (Matro et al., 2018). Another set of extracted data from the Pregnancy in Inflammatory Bowel Disease and Neonatal Outcomes registry (PIANO) registry was published in 2018 reporting infant serologic responses to HiB and tetanus vaccines after antenatal exposure to biologics including anti-TNFα and ustekinumab. The percentage of infants who had protective serological titers after HiB and tetanus vaccines did not differ between the exposed and non-exposed children, but the comparison group was small and included infants exposed to other immunosuppressive and immunomodulatory agents. Moreover, the response to vaccines was not related to the different titers of the biologics in cord blood at birth. Most of the mothers avoided the live-attenuated Rotavirus vaccine based on medical advice. Sequelae, including diarrhea and fever, were reported in 17% (7/40) of infants receiving the Rotavirus vaccine after exposure to anti-TNFα drugs (Beaulieu et al., 2018).

In an effort to determine the ability to achieve an adequate serological response after receiving an inactivated vaccine, de Lima et al. measured anti-hepatitis B antibodies one year after vaccination and proved that effective vaccination could be achieved in anti-TNFα exposed children similar to non-exposed children. Growth and developmental outcomes were also similar between the two groups at one year of age (de Lima et al., 2018). Recently a Korean study examined 12 children who were exposed to infliximab/adalimumab *in-utero* with a mean age of 28.3 ± 16.6 months. All showed average growth and development: 33% needed a booster dose after hepatitis B virus (HBV) vaccination for seroconversion which was similar to other non-exposed Korean children. Seven out of 12 children received live-attenuated vaccines before 6 months of age without complications (Lee et al., 2019).

Following the early discouraging results, BCG vaccine was given at different ages during the first year of life in various observational studies with generally few adverse events, but the relationship to the timing of the last dose of biologic therapy was sometimes poorly reported (Bortlik et al., 2014; Luu et al., 2018). Proper timing for BCG vaccination was investigated by retrospectively analyzing records of offspring of 74 women treated by anti-TNFα drugs during pregnancy, including those who received third trimester doses. Adverse events were very few and self-limited in infants who received BCG vaccine at a range of 0.25–11 months and totally absent in infants receiving it at or after the 6th month of age. The authors eventually recommended 6 months after birth as the optimal timing for delivering the BCG vaccine and the same recommendation may be applied to other live-attenuated vaccines (Park et al., 2020).

Few more results about some biologic drugs other than anti-TNFα are continuously published showing supporting evidence of long-term safety. Sixteen children were followed up to 1 year (6–48 weeks) after abatacept exposure in one study. No abnormal increase in infection rate or immunodeficiencies was observed (Kumar et al., 2015). Follow up of breastfed children exposed to anakinra since fetal stage and up to 10 years postnatal in some cases was mostly uneventful with no serious infections or developmental delays (Youngstein et al., 2017; Smith and Chambers, 2018). Response to vaccination after rituximab has been discussed in case reports. All showed adequate antibody responses to vaccines, including Tetanus, Diphtheria, HBV, HiB, MMR, and polio (Decker et al., 2006; Friedrichs et al., 2006; Mandal et al., 2014; Ling and Koren, 2016), except in one case report with an insufficient response after Diphtheria (Kimby et al., 2004).

INDIRECT EXPOSURE TO BIOLOGIC THERAPY VIA THE MALE PARTNER

A limited number of studies addressed paternal exposure to biological drugs, infertility, and pregnancy outcomes in the current literature. Cohort studies have reported no relevant

TABLE 4 | Characteristics of transfer of different biologics and their effect on the infants.

Drug	Placental transfer	Reported infant level at birth	Persistence in child blood after birth.	Transfer through breastfeeding	Reported child immunological changes	Relevant outcomes within the first year of life and vaccination responses[a]
Infliximab	Yes Julsgaard et al. (2016)	High, up to 2.6 infant to maternal ratio Kanis et al. (2018)	Persist for mean duration of 7.3 months Julsgaard et al. (2016)	Yes, at very low levels Matro et al. (2018)	In some cases, neutropenia, serious skin, bacterial and viral infections were reported Guiddir et al. (2014).	Overall, no serious adverse events Beaulieu et al. (2018).
Adalimumab	Yes Julsgaard et al. (2016)	High, up to 1.5 infant to maternal ratio Mahadevan et al. (2013)	Persists for mean duration of 4 months Julsgaard et al. (2016)	Yes, at very low levels Matro et al. (2018)	Altered T- and B-regulatory compartment, increased eosinophil counts in cord blood Esteve-Solé et al. (2017)	Abnormal infant's' immune response to BCG vaccine in one case of infliximab exposure Cheent et al. (2010).
Golimumab	Expected[b] Martin et al. (2007)	NA	Persists until 6 months in animal studies. Martin et al. (2007)	Very low Matro et al. (2018)	No reported immunological changes Martin et al. (2007)	Adequate serological response except for hemophilus influenza B and mumps vaccines after adalimumab exposure Duricova et al. (2019).
Etanercept	Low Berthelsen et al. (2010)	Cord blood level is negligible. Infant to maternal ratio is 0.04 Berthelsen et al. (2010)	-In one case, persisted for 3 months. Berthelsen et al. (2010)	Insignificant Murashima et al. (2009)	No reported immunological changes.	After rota virus vaccine, 17% of vaccinated children had diarrhea and fever Beaulieu et al. (2018).
Certolizumab	Almost no placental transfer Mariette et al. (2018)	Not detected/negligible infant to maternal ratio is 0 Mariette et al. (2018)	No Mariette et al. (2018)	Minimal/not detected Clowse et al. (2017)	No reported immunological changes	No reported abnormal growth or developmental changes.
Abatacept	Expected[b] Bristol-Myers Squibb (2017)	NA	NA	Very low Saito et al. (2019b)	No reported immunological changes	No adverse events were reported. No reported abnormal growth or developmental changes Saito et al. (2019b).
Rituximab	Yes (US Food and Drug Administ-ration, 2018)	Higher than maternal level Klink et al. (2008)	NA The biological effect persists up to 6 months due to its long half-life Østensen (2017)	Very low Bragnes et al. (2017)	Reversible decrease in infant total and B-cell lymphocytic counts Das et al. (2018)	Adequate antibody response to vaccines except in one case report with insufficient response after diphtheria Diphtheria. No reported abnormal growth or developmental changes. Kimby et al. (2004).
Belimumab	Yes GlaxoSmithKline, (2020)	NA	NA	Very low Saito et al. (2020)	Reversible decrease in infant total and B-cell lymphocytic counts Bitter et al. (2018)	Adequate responses with no adverse events. No reported abnormal growth or developmental changes Bitter et al. (2018); Saito et al. (2020).
Secukinumab	Expected[b] after 17th week Warren et al. (2018)	NA	NA	NA	NA	NA
Ixekizumab	Yes Clarke et al. (2015)	NA	NA	NA	NA	NA
Ustekinumab	Expected[b] (Gisbert and Chaparro (2020)	High, infant to maternal ratio up to 1.4–2:1 Mahadevan et al. (2017); Rowan et al. (2018)	NA	Very low Matro et al. (2018)	No reported immunological changes	NA on vaccine response No reported abnormal growth or developmental changes.
Tocilizumab	Yes, lower than other IgG molecules Moriyama et al. (2020)	Low drug levels were detected in cord blood Saito et al. (2019a).	Persists until 1–2 months Saito et al. (2019a)	Very low Saito et al. (2019a)	No reported immunological changes or severe infections.	No adverse events were reported. No reported abnormal growth or developmental changes Saito et al. (2019a).

(Continued on following page)

TABLE 4 | (*Continued*) Characteristics of transfer of different biologics and their effect on the infants.

Drug	Placental transfer	Reported infant level at birth	Persistence in child blood after birth.	Transfer through breastfeeding	Reported child immunological changes	Relevant outcomes within the first year of life and vaccination responses[a]
Anakinra	NA	NA	-NA	High Buescher and Malinowska, (1996).	No reported immunological changes or severe infections.	No adverse events were reported Duman et al. (2019). No reported abnormal growth or developmental changes up to 10 years.
Eculizumab	Yes, lower than IgG1 Eliesen et al. (2020b)	Not detected/very low cord blood level Sarno et al. (2019)	-NA	Undetectable Sarris et al. (2012)	No reported immunological changes normal infant complement activity	No adverse events were reported. No reported abnormal growth or developmental changes.
Denosumab	Yes Bussiere et al. (2013)	Detected in animal studies. Bussiere et al. (2013)	NA	Yes, likely low levels in breast milk in animal studies. Bussiere et al. (2013)	NA	NA

[a]*A lot of the vaccination reports did not include data about live-attenuated vaccines since they are usually delayed after 6 months of age.*
[b]*Expected based on the transfer of IgG1 molecules through placenta.*
NA: No available data.

difference between peri-conceptional paternal exposure to different anti-TNFα and undesirable pregnancy outcomes or congenital malformations with rates comparable to population rates (Viktil et al., 2012; Wallenius et al., 2015; Larsen et al., 2016).

The majority of papers reported no impact of TNFα inhibitors on male fertility (Saougou et al., 2013; Micu et al., 2014; Mouyis et al., 2019). Only a few reported decreased spermatozoa number or questionable abnormality of motility and morphology in relation to infliximab (Mahadevan et al., 2005; Montagna et al., 2005).

With other drugs, outcomes of 10, 54, and 13 pregnancies after paternal exposure to abatacept, secukinumab, and tocilizumab were satisfactory with the majority achieving healthy live births free of congenital anomalies (Kumar et al., 2015; Hoeltzenbein et al., 2016; Warren et al., 2018).

Followed pregnancies after rituximab treatment in the male partner were few. Only 9 of 22 pregnancies could be followed in one study with seven live births, four premature infants, and two spontaneous miscarriages (Chakravarty et al., 2011).

Unlike the EULAR recommendations in 2016 (Götestam Skorpen et al., 2016), the BSR-BHPR and the recent ACR guidelines devoted statements for prescribing antirheumatic drugs in male partners with SARD planning to conceive a pregnancy. Both guidelines recommended the continuation of infliximab, adalimumab, etanercept, and rituximab in men attempting to conceive. The BSR-BHPR did not make recommendations for certolizumab, and anakinra use in breastfeeding due to lack of supporting data, while the ACR guidelines strongly recommended certolizumab and conditionally recommended anakinra continuation (Flint et al., 2016; Sammaritano et al., 2020). Relevant recommendations for other biologics were not made due to limited data.

Table 4 summarizes the data on the transfer of the different biologicals and their effect on infants.

DISCUSSION

Ensuring safety of biological therapies during preconception, pregnancy, and breastfeeding offers an important treatment option in disorders in which disease control is crucial. Several reports and observational studies are reassuring especially in dealing with anti-TNFα therapies. Biologics may offer a safer choice than non-biologic drugs in regard to neonatal infections and congenital anomalies. Heterogeneity in study design, disease populations, target biologics studied, the timing of exposure to biologics, outcome measures, inadequate comparison groups and difficulty in adjustment for confounders such as disease activity do not provide very strong evidence for recommendations.

The largest experience is from IBD cases with exposure to anti-TNFα in pregnancy. TNFα inhibitors seem to be safe and effective without a significant maternal or fetal risk despite previous worries about the risk of an increase in congenital malformation. Except for certolizumab, a PEGylated monovalent Fab fragment, all other available anti-TNFα drugs cross the placental and can be detected in fetal blood. Eculizumab is another biologic which recently showed limited placental passage owing to the unique engineered structure of

IgG2/4. A comparable low placental transfer was described for etanercept as well because of its molecular structure. While some unfavorable pregnancy outcomes like low birth weight and preterm labor were reported with the use of biologics in pregnancy, it is arguable that they may be a consequence of the autoimmune disease itself. Evidence about the safety of other biologics has not yet been sufficient. Exposure through fathers has shown safe outcomes.

Some studies have reported alterations in maternal and infant immune systems; however, the whole spectrum of these changes and their effects need to be further evaluated. First-year tracking of exposed children is comforting. Live-attenuated vaccines are still avoided in clinical practice at least for the first 6 months of life due to the anticipated persistence of some mAbs. Proper timing of biological dosing in pregnancy is yet to be more clearly determined. Longer follow-up periods are still needed to monitor for possible late effects like the risk of malignancy and delayed immunological effects in the exposed children. Assessment of available biosimilar drugs' safety is also crucial since they provide more affordable therapy than biologic drugs. Only one paper published information about outcomes of a small number of pregnancies after peri-conceptional treatment by biosimilar infliximab with results not different from the original (Kolar et al., 2018).

Overall, the available data are encouraging. With the emergence of more studies every year, recommendations are stronger for considering treatment by certain biological drugs throughout gestation and breastfeeding.

AUTHOR CONTRIBUTIONS

AB and AA carried out the literature search; AB and PM wrote the paper; LT and WO discussed the obstetric aspects; AB and PM planned the review organization.

FUNDING

Ministero della Salute Ricerca Corrente 2019 to PLM-Istituto Auxologico Italiano. AB was supported by a grant from the Italian Ministry of Foreign Affairs and International Cooperation (MAECI) for foreign citizens and Italian citizens living abroad.

REFERENCES

Alijotas-Reig, J., Esteve-Valverde, E., Llurba, E., and Gris, J. M. (2019). Treatment of refractory poor aPL-related obstetric outcomes with TNF-alpha blockers: maternal-fetal outcomes in a series of 18 cases. *Semin. Arthritis Rheum.* 49 (2), 314–318. doi:10.1016/j.semarthrit.2019.02.006

Andreoli, L., Gerardi, M. C., Fernandes, M., Bortoluzzi, A., Bellando-Randone, S., Brucato, A., et al. (2019). Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. *Autoimmun. Rev.* 18 (2), 164–176. doi:10.1016/j.autrev.2018.08.008

Arsenescu, R., Arsenescu, V., and de Villiers, W. J. (2011). TNF-α and the development of the neonatal immune system: implications for inhibitor use in pregnancy. *Am. J. Gastroenterol.* 106 (4), 559. doi:10.1038/ajg.2011.5

Azim, H. A., Jr., Azim, H., and Peccatori, F. A. (2010). Treatment of cancer during pregnancy with monoclonal antibodies: a real challenge. *Expet Rev. Clin. Immunol.* 6 (6), 821–826. doi:10.1586/eci.10.77

Bazzani, C., Scrivo, R., Andreoli, L., Baldissera, E., Biggioggero, M., Canti, V., et al. (2015). Prospectively-followed pregnancies in patients with inflammatory arthritis taking biological drugs: an Italian multicentre study. *Clin. Exp. Rheumatol.* 33 (5), 688–693. PMID:26311348.

Beaulieu, D. B., Ananthakrishnan, A. N., Martin, C., Cohen, R. D., Kane, S. V., and Mahadevan, U. (2018). Use of biologic therapy by pregnant women with inflammatory bowel disease does not affect infant response to vaccines. *Clin. Gastroenterol. Hepatol.* 16 (1), 99–105. doi:10.1016/j.cgh.2017.08.041

Ben-Horin, S., Yavzori, M., Kopylov, U., Picard, O., Fudim, E., Eliakim, R., et al. (2011). Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *J. Crohns. Colitis.* 5 (6), 555–558. doi:10.1016/j.crohns.2011.05.006

Benson, J. M., Peritt, D., Scallon, B. J., Heavner, G. A., Shealy, D. J., Giles-Komar, J. M., et al. (2011). Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. *MAbs* 3 (6), 535–545. doi:10.4161/mabs.3.6.17815

Berthelsen, B. G., Fjeldsøe-Nielsen, H., Nielsen, C. T., and Hellmuth, E. (2010). Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology* 49 (11), 2225–2227. doi:10.1093/rheumatology/keq185

Bitter, H., Bendvold, A. N., and Østensen, M. E. (2018). Lymphocyte changes and vaccination response in a child exposed to belimumab during pregnancy. *Ann. Rheum. Dis.* 77 (11), 1692–1693. doi:10.1136/annrheumdis-2018-213004

Blair, H. A., and Deeks, E. D. (2017). Abatacept: a review in rheumatoid arthritis. *Drugs* 77 (11), 1221–1233. doi:10.1007/s40265-017-0775-4

Bortlik, M., Duricova, D., Machkova, N., Kozeluhova, J., Kohout, P., Hrdlicka, L., et al. (2014). Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm. Bowel Dis.* 20 (3), 495–501. doi:10.1097/01.MIB.0000440984.86659.4f

Bragnes, Y., Boshuizen, R., de Vries, A., Lexberg, Å., and Østensen, M. (2017). Low level of Rituximab in human breast milk in a patient treated during lactation. *Rheumatology* 56 (6), 1047–1048. doi:10.1093/rheumatology/kex039

Breedveld, F., Agarwal, S., Yin, M., Ren, S., Li, N. F., Shaw, T. M., et al. (2007). Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. *J. Clin. Pharmacol.* 47 (9), 1119–1128. doi:10.1177/0091270007305297

Brito-Zerón, P., Kostov, B., Bosch, X., Acar-Denizli, N., Ramos-Casals, M., and Stone, J. H. (2016). Therapeutic approach to IgG4-related disease: a systematic review. *Medicine* 95 (26), e4002. doi:10.1097/MD.0000000000004002

Bröms, G., Granath, F., Ekbom, A., Hellgren, K., Pedersen, L., Sørensen, H. T., et al. (2016). Low risk of birth defects for infants whose mothers are treated with anti-tumor necrosis factor Agents during pregnancy. *Clin. Gastroenterol. Hepatol.* 14 (2), 234–241.e5. doi:10.1016/j.cgh.2015.08.039

Buescher, E. S., and Malinowska, I. (1996). Soluble receptors and cytokine antagonists in human milk. *Pediatr. Res.* 40 (6), 839–844. doi:10.1203/00006450-199612000-00011

Burmester, G. R., Landewé, R., Genovese, M. C., Friedman, A. W., Pfeifer, N. D., Varothai, N. A., et al. (2017). Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 76 (2), 414–417. doi:10.1136/annrheumdis-2016-209322

Bussiere, J. L., Pyrah, I., Boyce, R., Branstetter, D., Loomis, M., Andrews-Cleavenger, D., et al. (2013). Reproductive toxicity of denosumab in cynomolgus monkeys. *Reprod. Toxicol.* 42, 27–40. doi:10.1016/j.reprotox.2013.07.018

Carman, W. J., Accortt, N. A., Anthony, M. S., Iles, J., and Enger, C. (2017). Pregnancy and infant outcomes including major congenital malformations among women with chronic inflammatory arthritis or psoriasis, with and without etanercept use. *Pharmacoepidemiol. Drug Saf.* 26 (9), 1109–1118. doi:10.1002/pds.4261

Carter, J. D., Valeriano, J., and Vasey, F. B. (2006). Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. *J. Rheumatol.* 33 (5), 1014–1017.

Casanova, M. J., Chaparro, M., Domènech, E., Barreiro-de Acosta, M., Bermejo, F., Iglesias, E., et al. (2013). Safety of thiopurines and anti-TNF-α drugs during pregnancy in patients with inflammatory bowel disease. *Am. J. Gastroenterol.* 108 (3), 433–440. doi:10.1038/ajg.2012.430

Chakravarty, E. F., Murray, E. R., Kelman, A., and Farmer, P. (2011). Pregnancy outcomes after maternal exposure to rituximab. *Blood* 117 (5), 1499–1506. doi:10.1182/blood-2010-07-295444

Chandran, V., van der Heijde, D., Fleischmann, R. M., Lespessailles, E., Helliwell, P. S., Kameda, H., et al. (2020). Ixekizumab treatment of biologic-naive patients with active psoriatic arthritis: 3-year results from a phase III clinical trial (SPIRIT-P1). *Rheumatology* 59 (10), 2774–2784. doi:10.1093/rheumatology/kez684

Chang, Z., Spong, C. Y., Jesus, A. A., Davis, M. A., Plass, N., Stone, D. L., et al. (2014). Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes (CAPS). *Arthritis Rheum.* 66 (11), 3227–3232. doi:10.1002/art.38811

Cheent, K., Nolan, J., Shariq, S., Kiho, L., Pal, A., and Arnold, J. (2010). Case Report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J. Crohns Colitis.* 4 (5), 603–605. doi:10.1016/j.crohns.2010.05.001

Clarke, D. O., Hilbish, K. G., Waters, D. G., Newcomb, D. L., and Chellman, G. J. (2015). Assessment of ixekizumab, an interleukin-17A monoclonal antibody, for potential effects on reproduction and development, including immune system function, in cynomolgus monkeys. *Reprod. Toxicol.* 58, 160–173. doi:10.1016/j.reprotox.2015.10.008

Clowse, M. E., Förger, F., Hwang, C., Thorp, J., Dolhain, R. J., van Tubergen, A., et al. (2017). Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann. Rheum. Dis.* 76 (11), 1890–1896. doi:10.1136/annrheumdis-2017-211384

Cooper, G. S., and Stroehla, B. C. (2003). The epidemiology of autoimmune diseases. *Autoimmun. Rev.* 2 (3), 119–125. doi:10.1016/s1568-9972(03)00006-5

Cooper, W. O., Cheetham, T. C., Li, D.-K., Stein, C. M., Callahan, S. T., Morgan, T. M., et al. (2014). Brief report: risk of adverse fetal outcomes associated with immunosuppressive medications for chronic immune-mediated diseases in pregnancy. *Arthritis Rheum.* 66 (2), 444–450. doi:10.1002/art.38262

Crijns, H. J., Jentink, J., Garne, E., Gispen-de Wied, C. C., Straus, S. M., and de Jong-van den Berg, L. T. (2011). The distribution of congenital anomalies within the VACTERL association among tumor necrosis factor antagonist-exposed pregnancies is similar to the general population. *J. Rheumatol.* 38 (9), 1871–1874. doi:10.3899/jrheum.101316

Dai, Y., Wang, W., Yu, Y., and Hu, S. (2020). Rheumatoid arthritis-associated interstitial lung disease: an overview of epidemiology, pathogenesis and management. *Clin. Rheumatol.* doi:10.1007/s10067-020-05320-z

Dall'ara, F., Reggia, R., Bazzani, C., Andreoli, L., Agosti, M., Mazza, G., et al. (2016). FRI0176 Safety of anti-TNF alfa agents during pregancy and breastfeeding: longterm follow up of exposed children in A case-series of mothers with chronic arthritides. *Ann. Rheum. Dis.* 75, 493. doi:10.1136/annrheumdis-2016-eular.4123

Danve, A., Perry, L., and Deodhar, A. (2014). Use of belimumab throughout pregnancy to treat active systemic lupus erythematosus: a case report. *Semin. Arthritis Rheum.* 44 (2), 195–197. doi:10.1016/j.semarthrit.2014.05.006

Das, G., Damotte, V., Gelfand, J. M., Bevan, C., Cree, B. A. C., Do, L., et al. (2018). Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. *Neurol. Neuroimmunol. Neuroinflamm.* 5 (3), e453. doi:10.1212/NXI.0000000000000453

de Lima, A., Kanis, S. L., Escher, J. C., and van der Woude, C. J. (2018). Hepatitis B vaccination effective in children exposed to anti-tumour necrosis factor Alpha in utero. *J. Crohns Colitis.* 12 (8), 948–953. doi:10.1093/ecco-jcc/jjy053

Decker, M., Rothermundt, C., Holländer, G., Tichelli, A., and Rochlitz, C. (2006). Rituximab plus CHOP for treatment of diffuse large B-cell lymphoma during second trimester of pregnancy. *Lancet Oncol.* 7 (8), 693–694. doi:10.1016/S1470-2045(06)70797-5

Diav-Citrin, O., Otcheretianski-Volodarsky, A., Shechtman, S., and Ornoy, A. (2014). Pregnancy outcome following gestational exposure to TNF-alpha-inhibitors: a prospective, comparative, observational study. *Reprod. Toxicol.* 43, 78–84. doi:10.1016/j.reprotox.2013.11.004

Duman, N. Ç., Gören, M. Z., and Karaalp, A. (2019). Anakinra use during pregnancy and lactation: a case report. *Reprod. Toxicol.* 88, 139–140. doi:10.1016/j.reprotox.2019.05.029

Duricova, D., Dvorakova, E., Hradsky, O., Mitrova, K., Durilova, M., Kozeluhova, J., et al. (2019). Safety of anti-TNF-alpha therapy during pregnancy on long-term outcome of exposed children: a controlled, multicenter observation. *Inflamm. Bowel Dis.* 25 (4), 789–796. doi:10.1093/ibd/izy294

Eliesen, G. A. M., van Drongelen, J., van Hove, H., Kooijman, N. I., van den Broek, P., de Vries, A., et al. (2020a). Assessment of placental disposition of infliximab and etanercept in women with autoimmune diseases and in the ex vivo perfused placenta. *Clin. Pharmacol. Ther.* 108 (1), 99–106. doi:10.1002/cpt.1827

Eliesen, G. A., van Drongelen, J., van den Broek, P. H., Sarlea, A., van der Heijden, O. W., Langemeijer, et al. (2020b). Placental disposition of eculizumab, C5 and C5-eculizumab in two pregnancies of a woman with paroxysmal nocturnal haemoglobinuria. *Br. J. Clin. Pharmacol.* 1, 4. doi:10.1111/bcp.14565

Esteve-Solé, A., Deyà-Martínez, À., Teixidó, I., Ricart, E., Gompertz, M., Torradeflot, M., et al. (2017). Immunological changes in blood of newborns exposed to anti-TNF-α during pregnancy. *Front. Immunol.* 8, 1123. doi:10.3389/fimmu.2017.01123

European Medicines Agency (2019). Cosentyx, INN-secukinumab. https://www.ema.europa.eu/en/documents/product-information/cosentyx-epar-product-information_en.pdf (Accessed August 24, 2020).

Fanouriakis, A., Kostopoulou, M., Alunno, A., Aringer, M., Bajema, I., Boletis, J. N., et al. (2019). 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann. Rheum. Dis.* 78 (6), 736–745. doi:10.1136/annrheumdis-2019-215089

Fava, A., and Petri, M. (2019). Systemic lupus erythematosus: diagnosis and clinical management. *J. Autoimmun.* 96, 1–13. doi:10.1016/j.jaut.2018.11.001

Fernández-Díaz, C., Castañeda, S., Melero-González, R. B., Ortiz-Sanjuán, F., Juan-Mas, A., Carrasco-Cubero, C., et al. (2020). Abatacept in interstitial lung disease associated with rheumatoid arthritis: national multicenter study of 263 patients. *Rheumatology* 59 (12), 3906–3916. doi:10.1093/rheumatology/keaa621

Firan, M., Bawdon, R., Radu, C., Ober, R. J., Eaken, D., Antohe, F., et al. (2001). The MHC class I-related receptor, FcRn, plays an essential role in the maternofetal transfer of gamma-globulin in humans. *Int. Immunol.* 13 (8), 993–1002. doi:10.1093/intimm/13.8.993

Flint, J., Panchal, S., Hurrell, A., van de Venne, M., Gayed, M., Schreiber, K., et al. (2016). BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology* 55 (9), 1693–1697. doi:10.1093/rheumatology/kev404

Förger, F., Zbinden, A., and Villiger, P. M. (2016). Certolizumab treatment during late pregnancy in patients with rheumatic diseases: low drug levels in cord blood but possible risk for maternal infections. a case series of 13 patients. *Joint Bone Spine* 83 (3), 341–343. doi:10.1016/j.jbspin.2015.07.004

Frieder, J., Kivelevitch, D., and Menter, A. (2018). Secukinumab: a review of the anti-IL-17A biologic for the treatment of psoriasis. *Ther. Adv. Chronic. Dis.* 9 (1), 5–21. doi:10.1177/2040622317738910

Friedrichs, B., Tiemann, M., Salwender, H., Verpoort, K., Wenger, M. K., and Schmitz, N. (2006). The effects of rituximab treatment during pregnancy on a neonate. *Haematologica* 91 (10), 1426–1427.

Gabriel, S. E., and Michaud, K. (2009). Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res. Ther.* 11 (3), 229. doi:10.1186/ar2669

Gasparoni, A., Avanzini, A., Ravagni Probizer, F., Chirico, G., Rondini, G., and Severi, F. (1992). IgG subclasses compared in maternal and cord serum and breast milk. *Arch. Dis. Child.* 67, 41–43. doi:10.1136/adc.67.1_spec_no.41

Geldhof, A., Slater, J., Clark, M., Chandran, U., and Coppola, D. (2020). Exposure to infliximab during pregnancy: post-marketing experience. *Drug Saf.* 43 (2), 147–161. doi:10.1007/s40264-019-00881-8

Genovese, M. C., Mysler, E., Tomita, T., Papp, K. A., Salvarani, C., Schwartzman, S., et al. (2020). Safety of ixekizumab in adult patients with plaque psoriasis, psoriatic arthritis and axial spondyloarthritis: data from 21 clinical trials. *Rheumatology* 59 (12), 3834–3844. doi:10.1093/rheumatology/keaa189

Giles, I., Yee, C.-S., and Gordon, C. (2019). Stratifying management of rheumatic disease for pregnancy and breastfeeding. *Nat. Rev. Rheumatol.* 15 (7), 391–402. doi:10.1038/s41584-019-0240-8

Gisbert, J. P., and Chaparro, M. (2020). Safety of new biologics (vedolizumab and ustekinumab) and small molecules (tofacitinib) during pregnancy: a review. *Drugs* 80 (11), 1085–1100. doi:10.1007/s40265-020-01346-4

GlaxoSmithKline (2020). Belimumab (BENLYSTA®) pregnancy registry. https://clinicaltrials.gov/ct2/show/NCT01532310 (Accessed August 12, 2020).

Götestam Skorpen, C., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., et al. (2016). The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheum. Dis.* 75 (5), 795–810. doi:10.1136/annrheumdis-2015-208840

Guiddir, T., Frémond, M. L., Triki, T. B., Candon, S., Croisille, L., Leblanc, T., et al. (2014). Anti–TNF-α therapy may cause neonatal neutropenia. *Pediatrics* 134 (4), e1189–93. doi:10.1542/peds.2014-0054

Gustavsen, A., Skattum, L., Bergseth, G., Lorentzen, B., Floisand, Y., Bosnes, V., et al. (2017). Effect on mother and child of eculizumab given before caesarean section in a patient with severe antiphospholipid syndrome: a case report. *Medicine* 96 (11), e6338. doi:10.1097/MD.0000000000006338

Hallstensen, R. F., Bergseth, G., Foss, S., Jæger, S., Gedde-Dahl, T., Holt, J., et al. (2015). Eculizumab treatment during pregnancy does not affect the complement system activity of the newborn. *Immunobiology* 220 (4), 452–459. doi:10.1016/j.imbio.2014.11.003

Hashira, S., Okitsu-Negishi, S., and Yoshino, K. (2000). Placental transfer of IgG subclasses in a Japanese population. *Pediatr. Int.* 42 (4), 337–342. doi:10.1046/j.1442-200x.2000.01245.x

Hatemi, G., Christensen, R., Bang, D., Bodaghi, B., Celik, A. F., Fortune, F., et al. (2018). 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann. Rheum. Dis.* 77 (6), 808–818. doi:10.1136/annrheumdis-2018-213225

Hoeltzenbein, M., Beck, E., Rajwanshi, R., Gøtestam Skorpen, C., Berber, E., Schaefer, C., et al. (2016). Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. *Semin. Arthritis Rheum.* 46 (2), 238–245. doi:10.1016/j.semarthrit.2016.05.004

Ijuin, A., Yoshikata, H., Asano, R., Tsuburai, T., Kikuchi, R., and Sakakibara, H. (2017). Teriparatide and denosumab treatment for pregnancy and lactation-associated osteoporosis with multiple vertebral fractures: a case study. Taiwan. *J. Obstet. Gynecol.* 56 (6), 863–866. doi:10.1016/j.tjog.2017.10.028

Jacobson, D. L., Gange, S. J., Rose, N. R., and Graham, N. M. (1997). Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin. Immunol. Immunopathol.* 84 (3), 223–243. doi:10.1006/clin.1997.4412

Jauniaux, E., Jurkovic, D., Gulbis, B., Liesnard, C., Lees, C., and Campbell, S. (1995). Materno-fetal immunoglobulin transfer and passive immunity during the first trimester of human pregnancy. *Hum. Reprod.* 10 (12), 3297–3300. doi:10.1093/oxfordjournals.humrep.a135906

Julsgaard, M., Christensen, L. A., Gibson, P. R., Gearry, R. B., Fallingborg, J., Hvas, C. L., et al. (2016). Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 151 (1), 110–119. doi:10.1053/j.gastro.2016.04.002

Junghans, R. P., and Anderson, C. L. (1996). The protection receptor for IgG catabolism is the beta2-microglobulin-containing neonatal intestinal transport receptor. *Proc. Natl. Acad. Sci. U.S.A.* 93 (11), 5512–5516. doi:10.1073/pnas.93.11.5512

Kane, S. V., and Acquah, L. A. (2009). Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am. J. Gastroenterol.* 104 (1), 228–233. doi:10.1038/ajg.2008.71

Kanis, S. L., de Lima-Karagiannis, A., van der Ent, C., Rizopoulos, D., and van der Woude, C. J. (2018). Anti-TNF levels in cord blood at birth are associated with anti-TNF type. *J. Crohns Colitis* 12 (8), 939–947. doi:10.1093/ecco-jcc/jjy058

Katz, J. A., Antoni, C., Keenan, G. F., Smith, D. E., Jacobs, S. J., and Lichtenstein, G. R. (2004). Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am. J. Gastroenterol.* 99 (12), 2385–2392. doi:10.1111/j.1572-0241.2004.30186.x

Keeling, S., and Wolbink, G. J. (2010). Measuring multiple etanercept levels in the breast milk of a nursing mother with rheumatoid arthritis. *J. Rheumatol.* 37 (7), 1551. doi:10.3899/jrheum.100077

Kelly, R., Arnold, L., Richards, S., Hill, A., Bomken, C., Hanley, J., et al. (2010). The management of pregnancy in paroxysmal nocturnal haemoglobinuria on long term eculizumab. *Br. J. Haematol.* 149 (3), 446–450. doi:10.1111/j.1365-2141.2010.08099.x

Kelly, R. J., Höchsmann, B., Szer, J., Kulasekararaj, A., de Guibert, S., Röth, A., et al. (2015). Eculizumab in pregnant patients with paroxysmal nocturnal hemoglobinuria. *N. Engl. J. Med.* 373 (11), 1032–1039. doi:10.1056/NEJMoa1502950

Kimby, E., Sverrisdottir, A., and Elinder, G. (2004). Safety of rituximab therapy during the first trimester of pregnancy: a case history. *Eur. J. Haematol.* 72 (4), 292–295. doi:10.1111/j.1600-0609.2004.00214.x

Klink, D. T., Van Elburg, R. M., Schreurs, M. W. J., and Van Well, G. T. J. (2008). Rituximab administration in third trimester of pregnancy suppresses neonatal B-cell development. *Clin. Dev. Immunol.* 2008, 1–6. doi:10.1155/2008/271363

Koenders, M. I., and van den Berg, W. B. (2016). Secukinumab for rheumatology: development and its potential place in therapy. *Drug Des. Dev. Ther.* 10, 2069–2080. doi:10.2147/DDDT.S105263

Kolar, M., Duricova, D., Bortlik, M., Lukas, M., Hruba, V., Machkova, N., et al. (2018). P614 Pregnancy outcomes in women with IBD treated with biosimilar infliximab. *J. Crohns Colitis.* 12 (Suppl. 1), S419–S420. doi:10.1093/ecco-jcc/jjx180.741

Kumar, M., Ray, L., Vemuri, S., and Simon, T. A. (2015). Pregnancy outcomes following exposure to abatacept during pregnancy. *Semin. Arthritis Rheum.* 45 (3), 351–356. doi:10.1016/j.semarthrit.2015.06.016

Kumthekar, A., Danve, A., and Deodhar, A. (2017). Use of belimumab throughout 2 consecutive pregnancies in a patient with systemic lupus erythematosus. *J. Rheumatol.* 44 (9), 1416–1417. doi:10.3899/jrheum.170327

Kuriya, B., Hernández-Díaz, S., Liu, J., Bermas, B. L., Daniel, G., and Solomon, D. H. (2011). Patterns of medication use during pregnancy in rheumatoid arthritis. *Arthritis Care Res.* 63 (5), 721–728. doi:10.1002/acr.20422

Larsen, M. D., Friedman, S., Magnussen, B., and Nørgård, B. M. (2016). Birth outcomes in children fathered by men treated with anti-TNF-α agents before conception. *Am. J. Gastroenterol.* 111 (11), 1608–1613. doi:10.1038/ajg.2016.405

Leach, J. L., Sedmak, D. D., Osborne, J. M., Rahill, B., Lairmore, M. D., and Anderson, C. L. (1996). Isolation from human placenta of the IgG transporter, FcRn, and localization to the syncytiotrophoblast: implications for maternal-fetal antibody transport. *J. Immunol.* 157 (8), 3317–3322

Lee, K. E., Jung, S. A., Park, S. H., Moon, C. M., Shim, S. Y., Kim, E. S., et al. (2019). Influence of anti-tumor necrosis factor-alpha therapy to pregnant inflammatory bowel disease women and their children's immunity. *Intest. Res.* 17 (2), 237–243. doi:10.5217/ir.2018.00071

Lichtenstein, G. R., Feagan, B. G., Mahadevan, U., Salzberg, B. A., Langholff, W., Morgan, J. G., et al. (2018). Pregnancy outcomes reported during the 13-year treat registry: a descriptive report. *Am. J. Gastroenterol.* 113 (11), 1678–1688. doi:10.1038/s41395-018-0202-9

Ling, J., and Koren, G. (2016). Challenges in vaccinating infants born to mothers taking immunoglobulin biologicals during pregnancy. *Expert Rev. Vaccines* 15 (2), 239–256. doi:10.1586/14760584.2016.1115351

Loza, M. J., Brodmerkel, C., Du Bois, R. M., Judson, M. A., Costabel, U., Drent, M., et al. (2011). Inflammatory profile and response to anti-tumor necrosis factor therapy in patients with chronic pulmonary sarcoidosis. *Clin. Vaccine Immunol.* 18 (6), 931–939. doi:10.1128/cvi.00337-10

Lozano, N. A., Lozano, A., Marini, V., Saranz, R. J., Blumberg, R. S., Baker, K., et al. (2018). Expression of FcRn receptor in placental tissue and its relationship with IgG levels in term and preterm newborns. *Am. J. Reprod. Immunol.* 80 (3), e12972. doi:10.1111/aji.12972

Lund, T., and Thomsen, S. F. (2017). Use of TNF-inhibitors and ustekinumab for psoriasis during pregnancy: a patient series. *Dermatol. Ther.* 30 (3), e12454. doi:10.1111/dth.12454

Luu, M., Benzenine, E., Doret, M., Michiels, C., Barkun, A., Degand, T., et al. (2018). Continuous anti-tnfα use throughout pregnancy: possible complications for the mother but not for the fetus. A retrospective cohort on the French national health insurance database (evasion). *Am. J. Gastroenterol.* 113 (11), 1669–1677. doi:10.1038/s41395-018-0176-7

Mahadevan, U., Cucchiara, S., Hyams, J. S., Steinwurz, F., Nuti, F., Travis, S. P. L., et al. (2011). The london position statement of the world congress of Gastroenterology on biological therapy for IBD with the European crohn's and colitis organisation: pregnancy and pediatrics. *Am. J. Gastroenterol.* 106 (2), 214–224. doi:10.1038/ajg.2010.464

Mahadevan, U., McConnell, R. A., and Chambers, C. D. (2017). Drug safety and risk of adverse outcomes for pregnant patients with inflammatory bowel disease. *Gastroenterology* 152 (29), 451–462. doi:10.1053/j.gastro.2016.10.013

Mahadevan, U., Terdiman, J. P., Aron, J., Jacobsohn, S., and Turek, P. (2005). Infliximab and semen quality in men with inflammatory bowel disease. *Inflamm. Bowel Dis.* 11 (4), 395–399. doi:10.1097/01.mib.0000164023.10848.c4

Mahadevan, U., Wolf, D. C., Dubinsky, M., Cortot, A., Lee, S. D., Siegel, C. A., et al. (2013). Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin. Gastroenterol. Hepatol.* 11 (3), 286–292. doi:10.1016/j.cgh.2012.11.011

Malek, A., Sager, R., Kuhn, P., Nicolaides, K. H., and Schneider, H. (1996). Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am. J. Reprod. Immunol.* 36 (5), 248–255. doi:10.1111/j.1600-0897.1996.tb00172.x

Mandal, P. K., Dolai, T. K., Bagchi, B., Ghosh, M. K., Bose, S., and Bhattacharyya, M. (2014). B cell suppression in newborn following treatment of pregnant diffuse large B-cell lymphoma patient with rituximab containing regimen. *Indian J. Pediatr.* 81 (10), 1092–1094. doi:10.1007/s12098-013-1336-9

Mariette, X., Förger, F., Abraham, B., Flynn, A. D., Moltó, A., Flipo, R. M., et al. (2018). Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann. Rheum. Dis.* 77 (2), 228–233. doi:10.1136/annrheumdis-2017-212196.

Martin, P. L., Cornacoff, J. B., Treacy, G., Eirikas, E., Marini, J., White, K. L., Jr., et al. (2008). Effects of administration of a monoclonal antibody against mouse tumor necrosis factor alpha during pregnancy and lactation on the pre- and postnatal development of the mouse immune system. *Int. J. Toxicol.* 27 (4), 341–347. doi:10.1080/10915810802368196

Martin, P. L., Oneda, S., and Treacy, G. (2007). Effects of an anti-TNF-α monoclonal antibody, administered throughout pregnancy and lactation, on the development of the macaque immune system. *Am. J. Reprod. Immunol.* 58 (2), 138–149. doi:10.1111/j.1600-0897.2007.00499.x

Matro, R., Martin, C. F., Wolf, D., Shah, S. A., and Mahadevan, U. (2018). Exposure concentrations of infants breastfed by women receiving biologic therapies for inflammatory bowel diseases and effects of breastfeeding on infections and development. *Gastroenterology* 155 (3), 696–704. doi:10.1053/j.gastro.2018.05.040

Maverakis, E., Marzano, A. V., Le, S. T., Callen, J. P., Brüggen, M. C., Guenova, E., et al. (2020). Pyoderma gangrenosum. *Nat. Rev. Dis. Primers.* 6 (1), 81. doi:10.1038/s41572-020-0213-x

Micu, M. C., Micu, R., Surd, S., Gîrlovanu, M., Bolboacă, S. D., and Ostensen, M. (2014). TNF-α inhibitors do not impair sperm quality in males with ankylosing spondylitis after short-term or long-term treatment. *Rheumatology* 53 (7), 1250–1255. doi:10.1093/rheumatology/keu007

Miyasaka, N., Miura, O., Kawaguchi, T., Arima, N., Morishita, E., Usuki, K., et al. (2016). Pregnancy outcomes of patients with paroxysmal nocturnal hemoglobinuria treated with eculizumab: a Japanese experience and updated review. *Int. J. Hematol.* 103 (6), 703–712. doi:10.1007/s12185-016-1946-x

Monaco, C., Nanchahal, J., Taylor, P., and Feldmann, M. (2015). Anti-TNF therapy: past, present and future. *Int. Immunol.* 27 (1), 55–62. doi:10.1093/intimm/dxu102

Montagna, G. L., Malesci, D., Buono, R., and Valentini, G. (2005). Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. *Ann. Rheum. Dis.* 64 (11), 1667. doi:10.1136/ard.2005.038620

Mor, G., and Cardenas, I. (2010). The immune system in pregnancy: a unique complexity. *Am. J. Reprod. Immunol.* 63 (6), 425–433. doi:10.1111/j.1600-0897.2010.00836.x

Moriyama, M., Wada, Y., Minamoto, T., Kondo, M., Honda, M., and Murakawa, Y. (2020). Unexpectedly lower proportion of placental transferred tocilizumab relative to whole immunoglobulin G: a case report. *Scand. J. Rheumatol.* 49 (2), 165–166. doi:10.1080/03009742.2019.1639821

Mouyis, M., Flint, J. D., and Giles, I. P. (2019). Safety of anti-rheumatic drugs in men trying to conceive: a systematic review and analysis of published evidence. *Semin. Arthritis Rheum.* 48 (5), 911–920. doi:10.1016/j.semarthrit.2018.07.011

Murashima, A., Watanabe, N., Ozawa, N., Saito, H., and Yamaguchi, K. (2009). Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. *Ann. Rheum. Dis.* 68 (11), 1793–1794. doi:10.1136/ard.2008.105924

Nakajima, K., Watanabe, O., Mochizuki, M., Nakasone, A., Ishizuka, N., and Murashima, A. (2016). Pregnancy outcomes after exposure to tocilizumab: a retrospective analysis of 61 patients in Japan. *Mod. Rheumatol.* 26 (5), 667–671. doi:10.3109/14397595.2016.1147405

Narula, N., Al-Dabbagh, R., Dhillon, A., Sands, B. E., and Marshall, J. K. (2014). Anti-tnfα therapies are safe during pregnancy in women with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm. Bowel Dis.* 20 (10), 1862–1869. doi:10.1097/MIB.0000000000000092

Nesbitt, A. M., Brown, D. T., Stephens, S., and Foulkes, R. (2006). Placental transfer and accumulation in milk of the anti-TNF antibody TN3 in rats: immunoglobulin G1 versus PEGylated Fab' :1119. *Am. J. Gastroenterol.* 101, S438. doi:10.14309/00000434-200609001-01119

Ngian, G. S., Briggs, A. M., Ackerman, I. N., and Van Doornum, S. (2016). Safety of anti-rheumatic drugs for rheumatoid arthritis in pregnancy and lactation. *Int J. Rheum Dis* 19, 834–843. doi:10.1111/1756-185X.12860

Nishimoto, N., and Kishimoto, T. (2008). "Humanized antihuman IL-6 receptor antibody, tocilizumab," in *Therapeutic antibodies*. Editors Y. Chernajovsky and A. Nissim (Berlin, Heidelberg: Springer), 181, 151–160. doi:10.1007/978-3-540-73259-4_7

Novartis Pharmaceuticals Corp (2020). COSENTYX® (secukinumab). https://www.novartis.us/sites/www.novartis.us/files/cosentyx.pdf (Accessed August 24, 2020).

Oddis, C. V., Reed, A. M., Aggarwal, R., Rider, L. G., Ascherman, D. P., Levesque, M. C., et al. (2013). Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum.* 65 (2), 314–324. doi:10.1002/art.37754

Okamatsu, N., Sakai, N., Karakawa, A., Kouyama, N., Sato, Y., Inagaki, K., et al. (2017). Biological effects of anti-RANKL antibody administration in pregnant mice and their newborns. *Biochem. Biophys. Res. Commun.* 491 (3), 614–621. doi:10.1016/j.bbrc.2017.07.154

Østensen, M. (2017). The use of biologics in pregnant patients with rheumatic disease. *Expet Rev. Clin. Pharmacol.* 10 (6), 661–669. doi:10.1080/17512433.2017.1305268

Pamfil, C., Fanouriakis, A., Damian, L., Rinzis, M., Sidiropoulos, P., Tsivgoulis, G., et al. (2015). EULAR recommendations for neuropsychiatric systemic lupus erythematosus vs usual care: results from two European centres. *Rheumatology* 54 (7), 1270–1278. doi:10.1093/rheumatology/keu482

Park, S. H., Kim, H. J., Lee, C. K., Song, E. M., Kang, S.-B., Jang, B. I., et al. (2020). Safety and optimal timing of BCG vaccination in infants born to mothers receiving anti-TNF therapy for inflammatory bowel disease. *J. Crohns Colitis.* 14 (12), 1780–1784. doi:10.1093/ecco-jcc/jjaa099

Petri, M. (2002). Epidemiology of systemic lupus erythematosus. *Best Pract. Res. Clin. Rheumatol.* 16 (5), 847–858. doi:10.1053/berh.2002.0259

Pham, T., Bachelez, H., Berthelot, J. M., Blacher, J., Claudepierre, P., Constantin, A., et al. (2012). Abatacept therapy and safety management. *Joint Bone Spine* 79 (Suppl. 1), 3–84. doi:10.1016/S1297-319X(12)70011-8

Porter, C., Armstrong-Fisher, S., Kopotsha, T., Smith, B., Baker, T., Kevorkian, L., et al. (2016). Certolizumab pegol does not bind the neonatal Fc receptor (FcRn): consequences for FcRn-mediated *in vitro* transcytosis and *ex vivo* human placental transfer. *J. Reprod. Immunol.* 116, 7–12. doi:10.1016/j.jri.2016.04.284

Porter, M. L., Lockwood, S. J., and Kimball, A. B. (2017). Update on biologic safety for patients with psoriasis during pregnancy. *Int. J. Womens. Dermatol.* 3 (1), 21–25. doi:10.1016/j.ijwd.2016.12.003

Puchner, A., Grochenig, H. P., Sautner, J., Helmy-Bader, Y., Juch, H., Reinisch, S., et al. (2019). Immunosuppressives and biologics during pregnancy and lactation: a consensus report issued by the austrian societies of gastroenterology and hepatology and rheumatology and rehabilitation. *Wien Klin. Wochenschr.* 131 (1–2), 29–44. doi:10.1007/s00508-019-1448-y

Pyzik, M., Sand, K. M. K., Hubbard, J. J., Andersen, J. T., Sandlie, I., and Blumberg, R. S. (2019). The neonatal Fc receptor (FcRn): a misnomer? *Front. Immunol.* 10, 1540. doi:10.3389/fimmu.2019.01540

Ramos-Casals, M., Brito-Zerón, P., Bombardieri, S., Bootsma, H., De Vita, S., Dörner, T., et al. (2020). EULAR recommendations for the management of Sjögren's syndrome with topical and systemic therapies. *Ann. Rheum. Dis.* 79 (1), 3–18. doi:10.1136/annrheumdis-2019-216114

Rovere-Querini, P., Canti, V., Erra, R., Bianchi, E., Slaviero, G., D'Angelo, A., et al. (2018). Eculizumab in a pregnant patient with laboratory onset of catastrophic

antiphospholipid syndrome: a case report. *Medicine* 97 (40), e12584. doi:10.1097/MD.0000000000012584

Rowan, C. R., Cullen, G., Mulcahy, H. E., Keegan, D., Byrne, K., Murphy, D. J., et al. (2018). Ustekinumab drug levels in maternal and cord blood in a woman with Crohn's disease treated until 33 weeks of gestation. *J. Crohns Colitis.* 12 (3), 376–378. doi:10.1093/ecco-jcc/jjx141

Rubbert-Roth, A., Furst, D. E., Nebesky, J. M., Jin, A., and Berber, E. (2018). A review of recent advances using tocilizumab in the treatment of rheumatic diseases. *Rheumatol. Ther.* 5 (1), 21–42. doi:10.1007/s40744-018-0102-x

Ryman, J. T., and Meibohm, B. (2017). Pharmacokinetics of monoclonal antibodies. CPT: CPT pharmacometrics syst. *Pharmacol* 6 (9), 576–588. doi:10.1002/psp4.12224

Saito, J., Yakuwa, N., Ishizuka, T., Goto, M., Yamatani, A., and Murashima, A. (2020). Belimumab concentrations in maternal serum and breast milk during breastfeeding and the safety assessment of the infant: a case study. *Breastfeed. Med.* 15 (7), 475–477. doi:10.1089/bfm.2020.0068

Saito, J., Yakuwa, N., Kaneko, K., Takai, C., Goto, M., Nakajima, K., et al. (2019a). Tocilizumab during pregnancy and lactation: drug levels in maternal serum, cord blood, breast milk and infant serum. *Rheumatology* 58 (8), 1505–1507. doi:10.1093/rheumatology/kez100

Saito, J., Yakuwa, N., Takai, C., Kaneko, K., Goto, M., Nakajima, K., et al. (2019b). Abatacept concentrations in maternal serum and breast milk during breastfeeding and an infant safety assessment: a case study. *Rheumatology* 58 (9), 1692–1694. doi:10.1093/rheumatology/kez135

Saji, F., Samejima, Y., Kamiura, S., and Koyama, M. (1999). Dynamics of immunoglobulins at the feto-maternal interface. *Rev. Reprod.* 4 (2), 81–89. doi:10.1530/ror.0.0040081

Sakurai, T., Takai, R., Bürgin, H., Ishihara, K., Sakamoto, Y., Amano, J., et al. (2012). The effects of interleukin-6 signal blockade on fertility, embryo-fetal development, and immunization *in vivo*. *Birth Defects Res. B. De.v Reprod. Toxicol.* 95 (4), 304–317. doi:10.1002/bdrb.21019

Sammaritano, L. R., Bermas, B. L., Chakravarty, E. E., Chambers, C., Clowse, M. E. B., Lockshin, M. D., et al. (2020). 2020 American college of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheum.* 72 (4), 529–556. doi:10.1002/art.41191

Sánchez, A., Zanchetta, M. B., and Danilowicz, K. (2016). Two cases of pregnancy- and lactation- associated osteoporosis successfully treated with denosumab. *Clin Cases Miner. Bone. Metab.* 13 (3), 244–246. doi:10.11138/ccmbm/2016.13.3.244

Saougou, I., Markatseli, T. E., Papagoras, C., Kaltsonoudis, E., Voulgari, P. V., and Drosos, A. A. (2013). Fertility in male patients with seronegative spondyloarthropathies treated with infliximab. *Joint Bone Spine* 80 (1), 34–37. doi:10.1016/j.jbspin.2012.03.004

Sarno, L., Tufano, A., Maruotti, G. M., Martinelli, P., Balletta, M. M., and Russo, D. (2019). Eculizumab in pregnancy: a narrative overview. *J. Nephrol.* 32 (1), 17–25. doi:10.1007/s40620-018-0517-z.

Sarris, I., Gandhi, S., Koumis, A., Elebute, M., Shehata, H., and Penna, L. (2012). Pregnancy outcome and safety of breast-feeding in two patients with paroxysmal nocturnal haemoglobinuria (PNH) treated with eculizumab. *Arch. Dis. Child Fetal Neonatal* 97 (Suppl. 1), A119. doi:10.1136/fetalneonatal-2012-301809.388

Schatz-Jakobsen, J. A., Zhang, Y., Johnson, K., Neill, A., Sheridan, D., and Andersen, G. R. (2016). Structural basis for eculizumab-mediated inhibition of the complement terminal pathway. *J. Immunol.* 197 (1), 337–344. doi:10.4049/jimmunol.1600280

Schirmer, M., Dejaco, C., and Duftner, C. (2012). Advances in the evaluation and classification of chronic inflammatory rheumatic diseases. *Discov. Med.* 13 (71), 299–304

Schmid, A. S., and Neri, D. (2019). Advances in antibody engineering for rheumatic diseases. *Nat. Rev. Rheumatol.* 15 (4), 197–207. doi:10.1038/s41584-019-0188-8

Schnitzler, F., Fidder, H., Ferrante, M., Ballet, V., Noman, M., Van Assche, G., et al. (2011). Outcome of pregnancy in women with inflammatory bowel disease treated with antitumor necrosis factor therapy. *Inflamm. Bowel Dis.* 17 (9), 1846–1854. doi:10.1002/ibd.21583

Seow, C. H., Leung, Y., Vande Casteele, N., Ehteshami Afshar, E., Tanyingoh, D., Bindra, G., et al. (2017). The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 45 (10), 1329–1338. doi:10.1111/apt.14040

Servais, A., Devillard, N., Frémeaux-Bacchi, V., Hummel, A., Salomon, L., Contin-Bordes, C., et al. (2016). Atypical haemolytic uraemic syndrome and pregnancy: outcome with ongoing eculizumab. *Nephrol. Dial. Transplant.* 31 (12), 2122–2130. doi:10.1093/ndt/gfw314

Shadick, N. A., Gerlanc, N. M., Frits, M. L., Stolshek, B. S., Brady, B. L., Iannaccone, C., et al. (2019). The longitudinal effect of biologic use on patient outcomes (disease activity, function, and disease severity) within a rheumatoid arthritis registry. *Clin. Rheumatol.* 38 (11), 3081–3092. doi:10.1007/s10067-019-04649-4

Shihab, Z., Yeomans, N. D., and De Cruz, P. (2016). Anti-Tumour necrosis factor α therapies and inflammatory bowel disease pregnancy outcomes: a meta-analysis. *J. Crohns Colitis.* 10 (8), 979–988. doi:10.1093/ecco-jcc/jjv234

Simister, N. E. (2003). Placental transport of immunoglobulin G. *Vaccine* 21 (24), 3365–3369. doi:10.1016/s0264-410x(03)00334-7

Simister, N. E., Story, C. M., Chen, H. L., and Hunt, J. S. (1996). An IgG-transporting Fc receptor expressed in the syncytiotrophoblast of human placenta. *Eur. J. Immunol.* 26 (7), 1527–1531. doi:10.1002/eji.1830260718

Smith, C. J. F., and Chambers, C. D. (2018). Five successful pregnancies with antenatal anakinra exposure. *Rheumatology* 57 (7), 1271–1275. doi:10.1093/rheumatology/key093

So, A., Dumusc, A., and Nasi, S. (2018). The role of IL-1 in gout: from bench to bedside. *Rheumatology* 57 (Suppl. 1), i12–i19. doi:10.1093/rheumatology/kex449

Squibb, B.-M (2017). Orencia prescribing information. https://packageinserts.bms.com/pi/pi_orencia.pdf (Accessed September 5, 2020).

Squibb, B.-M (2019). Abatacept pregnancy exposure registry. https://clinicaltrials.gov/ct2/show/NCT01087125 (Accessed September 5, 2020).

Stefanovic, V. (2019). The extended use of eculizumab in pregnancy and complement Activation-Associated diseases affecting maternal, fetal and neonatal kidneys-the future is now? *J. Clin. Med.* 8 (3), 407. doi:10.3390/jcm8030407

Stolyar, L., Lahita, R. G., and Panush, R. S. (2020). Rituximab use as induction therapy for lupus nephritis: a systematic review. *Lupus* 29 (8), 892–912. doi:10.1177/0961203320928412

Strohl, W. R., and Strohl, L. M. (2012). "1—Introduction to biologics and monoclonal antibodies," in *Therapeutic antibody engineering*. Editors W. R. Strohl and L. M. Strohl (Cambridge, United Kingdom: Woodhead Publishing), 1–595

Tada, Y., Sakai, M., Nakao, Y., Maruyama, A., Ono, N., and Koarada, S. (2019). Placental transfer of tocilizumab in a patient with rheumatoid arthritis. *Rheumatology* 58 (9), 1694–1695. doi:10.1093/rheumatology/kez155

Thurlings, R. M., Teng, O., Vos, K., Gerlag, D. M., Aarden, L., Stapel, S. O., et al. (2010). Clinical response, pharmacokinetics, development of human anti-chimaeric antibodies, and synovial tissue response to rituximab treatment in patients with rheumatoid arthritis. *Ann. Rheum. Dis.* 69 (2), 409–412. doi:10.1136/ard.2009.109041

Treacy, G. (2000). Using an analogous monoclonal antibody to evaluate the reproductive and chronic toxicity potential for a humanized anti-TNFalpha monoclonal antibody. *Hum. Exp. Toxicol.* 19 (4), 226–228. doi:10.1191/096032700678815765

US Food and Drug Administration (2019b). ACTEMRA® (tocilizumab). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125276s127,125472s040lbl.pdf (Accessed July 20, 2020).

US Food and Drug Administration (2008). Arcalyst (rilonacept) label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125249lbl.pdf (Accessed September 1, 2020).

US Food and Drug Administration (2019c). BENLYSTA® (belimumab). https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125370s064,761043s007lbl.pdf (Accessed August 12, 2020).

US Food and Drug Administration (2017a). ORENCIA (abatacept). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125118s209lbl.pdf (Accessed August 25, 2020).

US Food and Drug Administration (2012). RITUXAN (rituximab). https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103705s5367s5388lbl.pdf (Accessed August 10, 2020).

US Food and Drug Administration (2017b). SOLIRIS® (eculizumab). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125166s422lbl.pdf (Accessed August 10, 2020).

US Food and Drug Administration (2019a). Stelara (ustekinumab). https://www.drugs.com/newdrugs/fda-approves-stelara-ustekinumab-adults-moderately-severely-active-crohn-s-4436.html (Accessed September 1, 2020).

Venhoff, N., Voll, R. E., Glaser, C., and Thiel, J. (2018). [IL-1-blockade with Anakinra during pregnancy : retrospective analysis of efficacy and safety in female patients with familial Mediterranean fever]. *Z. Rheumatol.* 77 (2), 127–134. doi:10.1007/s00393-017-0354-9

Venturin, C., Nancey, S., Danion, P., Uzzan, M., Chauvenet, M., Bergoin, C., et al. (2017). Fetal death in utero and miscarriage in a patient with Crohn's disease under therapy with ustekinumab: case-report and review of the literature. *BMC Gastroenterol.* 17 (1), 80. doi:10.1186/s12876-017-0633-6

Verstappen, S. M., King, Y., Watson, K. D., Symmons, D. P., and Hyrich, K. L. (2011). Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British society for rheumatology biologics register. *Ann. Rheum. Dis.* 70 (5), 823–826. doi:10.1136/ard.2010.140822

Viktil, K. K., Engeland, A., and Furu, K. (2012). Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. *Scand. J. Rheumatol.* 41 (3), 196–201. doi:10.3109/03009742.2011.626442

Vitale, A., Insalaco, A., Sfriso, P., Lopalco, G., Emmi, G., Cattalini, M., et al. (2016). A snapshot on the on-label and off-label use of the interleukin-1 inhibitors in Italy among rheumatologists and pediatric rheumatologists: a nationwide multi-center retrospective observational study. *Front. Pharmacol.* 7, 380. doi:10.3389/fphar.2016.00380

Wallenius, M., Lie, E., Daltveit, A. K., Salvesen, K., Skomsvoll, J. F., Kalstad, S., et al. (2015). No excess risks in offspring with paternal preconception exposure to disease-modifying antirheumatic drugs. *Arthritis Rheum.* 67 (1), 296–301. doi:10.1002/art.38919

Ward, M., and Tektonidou, M. G. (2020). Belimumab as add-on therapy in lupus nephritis. *N. Engl. J. Med.* 383 (12), 1184–1185. doi:10.1056/NEJMe2027516

Warren, R. B., Reich, K., Langley, R. G., Strober, B., Gladman, D., Deodhar, A., et al. (2018). Secukinumab in pregnancy: outcomes in psoriasis, psoriatic arthritis and ankylosing spondylitis from the global safety database. *Br. J. Dermatol.* 179 (5), 1205–1207. doi:10.1111/bjd.16901

Watson, N., Wu, K., Farr, P., Reynolds, N. J., and Hampton, P. J. (2019). Ustekinumab exposure during conception and pregnancy in patients with chronic plaque psoriasis: a case series of 10 pregnancies. *Br. J. Dermatol.* 180 (1), 195–196. doi:10.1111/bjd.17086.

Weber-Schoendorfer, C., Oppermann, M., Wacker, E., Bernard, N., Beghin, D., Cuppers-Maarschalkerweerd, B., et al. (2015). Pregnancy outcome after TNF-α inhibitor therapy during the first trimester: a prospective multicentre cohort study. *Br. J. Clin. Pharmacol.* 80 (4), 727–739. doi:10.1111/bcp.12642

Weber-Schoendorfer, C., and Schaefer, C. (2016). Pregnancy outcome after tocilizumab therapy in early pregnancy-a case series from the German embryotox pharmacovigilance center. *Reprod. Toxicol.* 60, 29–32. doi:10.1016/j.reprotox.2016.01.002

Wood, G. W., Bjerrum, K., and Johnson, B. (1982). Detection of IgG bound within human trophoblast. *J. Immunol.* 129 (4), 1479–1484.

Wu, T. Y., and Ying, K. Y. (2019). Disease modifying anti-rheumatic drugs: review on pregnancy and lactation. *JCRI* 19 (1), 18–26. doi:10.1142/S2661341719500020

Yates, M., Watts, R. A., Bajema, I. M., Cid, M. C., Crestani, B., Hauser, T., et al. (2016). EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann. Rheum. Dis.* 75 (9), 1583–1594. doi:10.1136/annrheumdis-2016-209133

Youngstein, T., Hoffmann, P., Gül, A., Lane, T., Williams, R., Rowczenio, D. M., et al. (2017). International multi-centre study of pregnancy outcomes with interleukin-1 inhibitors. *Rheumatology* 56 (12), 2102–2108. doi:10.1093/rheumatology/kex305.

Zelikin, A. N., Ehrhardt, C., and Healy, A. M. (2016). Materials and methods for delivery of biological drugs. *Nat. Chem.* 8 (11), 997–1007. doi:10.1038/nchem.2629

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling Editor declared a past co-authorship with one of the authors PM.

frontiers in Pharmacology

REVIEW
published: 18 March 2021
doi: 10.3389/fphar.2021.626258

The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children's Outcome

Cecilia Nalli[1], Jessica Galli[2], Daniele Lini[1,3], Angela Merlini[2], Silvia Piantoni[1,3], Maria Grazia Lazzaroni[1,3], Victoria Bitsadze[4], Jamilya Khizroeva[4], Sonia Zatti[5], Laura Andreoli[1,3], Elisa Fazzi[2], Franco Franceschini[1,3], Alexander Makatsariya[4], Yehuda Shoenfeld[6,7,8] and Angela Tincani[1,3,8]*

[1]Rheumatology and Clinical Immunology Unit, ASST Spedali Civili and University of Brescia, Brescia, Italy, [2]Child Neurology and Psychiatry Unit, Department of Clinical and Experimental Sciences, ASST Spedali Civili and University of Brescia, Brescia, Italy, [3]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, [4]Department of Obstetrics and Gynecology, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia, [5]Obstetric and Gynecology Unit, ASST Spedali Civili of Brescia, Brescia, Italy, [6]Department of Medicine 'B', The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Ramat Gan, Israel, [7]Sackler Faculty of Medicine, Tel-Aviv University, Tel Aviv-Yafo, Israel, [8]I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia

OPEN ACCESS

Edited by:
Cecilia Beatrice Chighizola, Istituto Auxologico Italiano (IRCCS), Italy

Reviewed by:
Frauke Förger, Inselspital, Bern, Switzerland
Gabriele Simonini, University of Florence, Italy

***Correspondence:**
Cecilia Nalli
cecilianalli2@gmail.com

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *05 November 2020*
Accepted: *29 January 2021*
Published: *18 March 2021*

Citation:
Nalli C, Galli J, Lini D, Merlini A, Piantoni S, Lazzaroni MG, Bitsadze V, Khizroeva J, Zatti S, Andreoli L, Fazzi E, Franceschini F, Makatsariya A, Shoenfeld Y and Tincani A (2021) The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children's Outcome. Front. Pharmacol. 12:626258. doi: 10.3389/fphar.2021.626258

The management of reproductive issues in women with inflammatory arthritis has greatly changed over decades. In the 1980–1990s, women with refractory forms of arthritis were either not able to get pregnant or did choose not to get pregnant because of their disabling disease. Hence, the traditional belief that pregnancy can induce a remission of arthritis. The availability of biologic agents has allowed a good control of aggressive forms of arthritis. The main topic of discussion during preconception counselling is the use of drugs during pregnancy and breastfeeding. Physicians are now supported by international recommendations released by the European League Against Rheumatism and the American College of Rheumatology, but still they must face with cultural reluctance in accepting that a pregnant woman can take medications. Patient-physician communication should be centered on the message that active maternal disease during pregnancy is detrimental to fetal health. Keeping maternal disease under control with drugs which are not harmful to the fetus is the best way to ensure the best possible outcome for both the mother and the baby. However, there might be concerns about the influence of the *in utero* exposure to medications on the newborn's health conditions. Particularly, studies suggesting an increased risk of autism-spectrum-disorders in children born to women with rheumatoid arthritis has raised questions about neuropsychological impairment in the offspring of women with chronic arthritis. As a multidisciplinary group of rheumatologists and child neuropsychiatrists, we conducted a study on 16 women with chronic forms of arthritis whose diagnosis was determined before pregnancy and their 18 school-age children. The children underwent a complete neurological examination and validated tests/questionnaires. Behavioral aspects of somatization and anxiety/depression (internalizing problem) or an "adult profile" were found in nearly one third of children. Children at a high

risk of neurodevelopmental problems were born to mothers with a longer history of arthritis and were breastfeed for less than 6 months of age or were not breastfeed at all. No association was found with other maternal characteristics such as autoantibody existence and disease activity during and after the pregnancy.

Keywords: rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, pregnancy, immunosuppressants, children's development

INTRODUCTION

In the past decades, young women affected by chronic inflammatory arthritis were discouraged of a pregnancy due to the joint pains, fatigue, disability, skeletal deformity and the loss of self-esteem. As a matter of fact, these women have a smaller family size as compared not only with the general population but also with patients with other rheumatic diseases (Østensen, 2004). Nowadays, the general health status of patients with inflammatory arthritis has greatly improved due to the introduction, nearly 20 years ago, of new treatments that are able to switch off inflammation and consequently to control the symptoms and joint damage. Despite this improvement in management, the approach to reproductive issues is an unmet need as a reduced family size has been still observed in men and women with rheumatic diseases (Østensen, 2017b). Several different reasons underlie this phenomenon: disease activity, impaired sexual function, personal choices, and an increased rate of pregnancy loss, even if this problem is not as frequent in patients with inflammatory arthritis as in other rheumatic diseases.

An additional important issue is related to the need of treatment during pregnancy. In an ideal situation, women with inflammatory arthritis should become pregnant when the disease is in a stable remission thanks to the administration of an effective therapy. Treatment should be ideally continued throughout the pregnancy to ensure good outcomes. In fact, in contrast to what was described before the 1990s, we now are aware that pregnancy "*per se*" is not able to induce remission in all the patients with inflammatory arthritis (Østensen et al., 1983).

According to a recent metanalysis published in 2019, nearly 40% of the patients experience a remission state during pregnancy (Atta et al., 2016; Jethwa et al., 2019). Therefore, the majority of the women with inflammatory arthritis can have flares during pregnancy and need to be treated even if pregnancy was initiated in a remission phase. Obviously, this rule will be more stringent when pregnancy took place in a period of active disease, even if this is a relatively rare event because of the above-mentioned reasons. Pregnant women with inflammatory arthritis have an increased need for treatment today than in the past. This situation is related to the fact that pregnancy generally occurs along with patient's well-being that in the past was achieved only in relatively mild situations responding to traditional drugs. Nowadays, also patients with an aggressive arthritis can reach a well-being state and start a pregnancy if adequately treated with effective biological drugs (Giles et al., 2019).

In these conditions, the known decrease in Th1 activity will not be enough to keep the disease in remission (Østensen et al., 2005).

On the other hand, the puerperium has always been known as a period with a high risk of flares for patients with inflammatory arthritis (Jethwa et al., 2019). This can be particularly frustrating since the mothers need to feel good to look after the newborn. The feeling of being inadequate in taking care of the newborn can facilitate the development of postpartum depression. Therefore, disease control must be achieved with drugs that are compatible with breastfeeding (Ince-Askan et al., 2019a).

The hardest task for the physician is to convince pregnant and nursing patients that taking "safe" drugs is a way to take care of the baby's wellbeing. If the mother feels well, then the baby will be OK too. Reassuring data about the health and growth conditions of children antenatally exposed to anti-rheumatic drugs are useful for counselling (Bortoluzzi et al., 2021).

This article aims at reviewing the literature and report our experience on the long-term follow-up of children born to patients with inflammatory arthritis exposed to anti-rheumatic drugs before and during pregnancy and breastfeeding.

THE USE OF ANTI-RHEUMATIC DRUGS DURING PREGNANCY

The control of disease activity is fundamental for a successful pregnancy. In fact, high disease activity is associated with an increased risk of pregnancy complications and adverse outcomes, including preeclampsia, preterm delivery, low birth weight, small for gestational age, and fetal loss (Østensen, 2017a). According to the published data, even if no randomized clinical trials are available in the field of pregnancy, an effective treatment of chronic arthritis is possible with an acceptable safety profile during pregnancy and lactation. The dissemination of this evidence among health professionals and patients is important in order to improve the management of pregnant and lactating mothers with rheumatic diseases.

In 2016, the European League Against Rheumatism (EULAR), and in 2020, the American College of Rheumatology (ACR), published recommendations for a safe use of anti-rheumatic drugs before and during pregnancy and lactation (Götestam Skorpen et al., 2016; Sammaritano et al., 2020). The same was done by the British Society of Rheumatology (Flint et al., 2016a; Flint et al., 2016b).

To date, the available data from the literature and from registries showed that a great number of drugs can be taken by pregnant and lactating women without causing harm to the children in terms of congenital malformations and miscarriages. Glucocorticoids, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, colchicine, cyclosporine, tacrolimus and

intravenous immunoglobulins (IvIg) were reported to be compatible with pregnancy and lactation.

The data about non-steroidal anti-inflammatory drugs in pregnancy are conflicting but, in general, non-selective COX inhibitors are preferable.

Methotrexate, mycophenolate mofetil and cyclophosphamide must be discontinued before conception due to their proven teratogenicity.

Even though biologics have shown efficacy in keeping the disease under control, their safety profile in pregnant women is still under investigation. A recent meta-analysis on this topic found no association between the use of biologics during pregnancy and the risk of congenital malformation, preterm deliveries or serious infections requiring hospitalization in infants' first year of life, compared with disease-matched unexposed pregnant women (Tsao et al., 2020). The use of adalimumab (ADA), certolizumab pegol (CTZ), infliximab (IFX), and etanercept (ETA) during pregnancy is now widely accepted if clearly needed, based on the results of the pregnancy registries (Ghalandari et al., 2020). All the TNFα inhibitors showed a good safety profile if used in the first half of pregnancy. In fact, even if they differ in their molecular structure, they are all of big molecular size proteins which cannot passively diffuse and reach the fetus during the first trimester of gestation. Based on this assumption, unintended pregnancies exposed to these drugs should not raise any concern. Moreover, it is currently suggested to maintain the treatment during pregnancy, as their discontinuation at a positive pregnancy index has been associated with maternal disease flares during pregnancy (and poorer pregnancy outcomes as a consequence) (Van den Brandt et al., 2017).

Considering their molecular structure which influences their placental transfer, IFX, ADA and ETA may preferentially be discontinued in the second/third trimester. In fact, active transplacental transport of immunoglobulin G (IgG) from mother to infant is mediated by the neonatal receptor for the crystallizable (FcRn), a process that takes place mainly during the second and third trimesters of pregnancy. Differently from the others, CTZ cannot be transferred across the placenta, because it lacks IgG Fc region. For this reason, it has a safer profile during pregnancy with specific studies showing minimal to no transfer into neonatal blood and breastmilk (Clowse et al., 2018; Mariette et al., 2018). Evidence for safety is still scarce for leflunomide, tofacitinib as well as golimumab, abatacept, tocilizumab, ustekinumab, rituximab (RTX), anakinra and canakinumab. Even if no alerts were published about their use before conception or in the first trimester, the general advice is to discontinue their use before a planned pregnancy (Götestam Skorpen et al., 2016; Sammaritano et al., 2020), but the progressive increase of available data could change this attitude, as it has happened for the TNFα inhibitors.

Regarding the use of rituximab in selected severe cases of arthritis, the recommendation is to continue the treatment until conception/early during the first trimester but also during pregnancy in the presence of severe maternal disease. There are no data suggesting teratogenic effects for exposure to RTX during the first trimester, while second/third-trimester exposure is associated with neonatal B cell depletion (Flint et al., 2016a).

The high rate of pregnancies without known outcomes and the high number of lost to follow-up limit the potentiality of global clinical safety databases (Sinclair et al., 2014). The data available for azathioprine, cyclosporine and dexamethasone do not indicate immunosuppression in the exposed children; on the contrary, the administration of biologics after gestational week 30 might increase the risk of postnatal infection (Giles et al., 2019). However, the children exposed to biologics before the week 22 can receive vaccinations according with the standard protocols (Furer et al., 2020). Pharmacological properties of drugs act as a guide for decision to allow breastfeeding, considering the insufficient and heterogeneous documentation regarding clinical practice (Flint et al., 2016a; Götestam Skorpen et al., 2016).

LIGHTS AND SHADOWS ABOUT THE PRESCRIPTION OF ANTI-RHEUMATIC DRUGS TO PREGNANT WOMEN WITH INFLAMMATORY ARTHRITIS

Women suffering from severe arthritis during pregnancy and who were offered to take drugs to relieve their pains often answer, "I will stay in bed for 9 months and bear all the pain of the world, but I do not want to cause any harm to my baby by taking drugs!." This widespread attitude is driven by the rooted belief that any drug taken during gestation can be harmful to the child. It is no easy task for the physicians to convince the patient otherwise; much has still to be achieved in the physician-patient communication about the use of drugs during pregnancy.

The patients' knowledge about the compatibility of drugs during pregnancy is extremely limited. According to a recent national survey performed in Italy (Andreoli et al., 2019), even patients with previous successful pregnancies occurring after the disease onset had discordant opinions about this topic. In fact, several of them were not aware of the safety of drugs commonly offered to treat arthritis during pregnancy. As an example, about 30% of the patients did not know that hydroxychloroquine can be taken during pregnancy and lactation without any harm to the child. These findings underline the need of young women with inflammatory arthritis of an exhaustive counselling focusing on reproductive issues but, in particular, on the consequence of treating or not treating their disease (Chew et al., 2019).

Physicians must empower their skills in performing counselling. It is first necessary to clarify to the patients that active arthritis can interfere with fetal growth and cause preterm delivery and small for gestational age infants together with other less frequent pregnancy complications (Andreoli et al., 2019). In contrast with the traditional belief that pregnancy related immunomodulation was able to induce disease remission at least in patients affected by RA, several recent reports underlined that this is true only for a part of the patients, while flares during gestation are recorded in about 29% of

TABLE 1 | Classification of drug administration to pregnant patients with inflammatory arthritis and their restrictions during pregnancy [adapted from Østensen (2017a)].

Drugs to be stopped before pregnancy	Drugs with insufficient data	Drugs that can be used in pregnancy
Methotrexate (stop at least 3 months before a planned pregnancy), Cyclophosphamide (stop at least 3 months before a planned pregnancy), Mycophenolate Mofetil (stop at least 6 weeks before a planned pregnancy), Warfarin/acenocumarol (discontinuation at positive pregnancy test).	Leflunomide, Mepacrine, Biologic agents other than anti-TNF alfa inhibitors (e.g., rituximab, anakinra, tocilizumab, abatacept, belimumab, ustekinumab), JAK inhibitors, Selective COX-2 inhibitors.	Steroids (oral, intra-articular and intravenous pulses[a]), Hydroxychloroquine, Chloroquine, NSAIDs (until 32 weeks of gestation), Azathioprine, Cyclosporine, Tacrolimus, Sulfasalazine, Colchicine, Intravenous immunoglobulins[a], anti-TNF alfa inhibitors.

Abbreviations: anti TNF, anti-tumor necrosis factor; NSAIDs, nonsteroidal anti-inflammatory drug.
[a]*For severe organ involvement.*

patients with RA and 25% of patients with axial spondyloarthropathy (Zbinden et al., 2018). A significantly increased risk of flares is linked to the presence of active disease at conception and to the withdrawal of effective treatments at the beginning of pregnancy. According to these findings, the refusal to take drugs during pregnancy will not favor the baby's health, but will rather deteriorate the mother's joints (with the consequent difficulties in neonatal caregiving) and will increase the risk for adverse pregnancy outcomes that can negatively affect the baby's health. The second aspect is related to the safety of the drugs to be administered in pregnancy. As detailed in the previous paragraph, many drugs routinely employed in Rheumatology are compatible with pregnancy while very few need to be withdrawn before conception because of their possible teratogenicity (Ahmed et al., 2020).

To make the issue easily understandable to patients, it is possible to classify anti-rheumatic drugs used to treat inflammatory arthritis into three categories: 1) drugs that can be continued during pregnancy, 2) drugs that need to be withdrawn, and 3) drugs with no evidence of harm but without sufficient experience for confirming their safety (**Table 1**). The drugs recently introduced in clinical practice belong to the third group and their administration in pregnant women need to be carefully evaluated by considering the risk/benefit balance in the individual case.

Counselling should include also a discussion about the post-partum period. Patients with RA or spondyloarthropathy must be aware of the high risk of flares (Jethwa et al., 2019) during this delicate period in which they are expected to be able to take care of the newborn. About half of the women affected by RA reported a worsening of joint pain after delivery (Eudy et al., 2018). To explain the high rate of flares observed in the weeks after delivery, some authors focused on the possible effect of high levels of prolactin (Borba et al., 2019) and discussed situations in which breastfeeding should be discouraged (Vieira Borba and Shoenfeld, 2019). However, the recently published ACR guidelines (Sammaritano et al., 2020) underline the benefits of breastfeeding for both the baby and the mother. Therefore, the guidelines recommend encouraging breastfeeding by achieving a good disease control with compatible medications, highlighting the need for more scientific evidence in this specific area. In this respect, a very recent publication underlines the benefit of breast feeding on the neonate immune system: the exposure of children to maternal cells even for a short time was shown to enhance the maturation of neonate T regulatory cells (Wood et al., 2020).

THE OUTCOME OF CHILDREN BORN TO MOTHERS WITH INFLAMMATORY ARTHRITIS AND ANTENATALLY EXPOSED TO ANTI-RHEUMATIC DRUGS

Outcomes Related to Disease

The information on the children born to mother affected by rheumatic diseases are mainly accumulated by national and international registries. A recent report focuses on the RAPPORT registry, a retrospective anonymous RedCAP survey of peripartum period in females with RA/Psoriatic Arthritis (PsA). Authors collected data on 234 pregnancies (103 patients), 164 pregnancies before and 70 pregnancies after the disease onset. The results included: 96% live births, 1.9% stillbirths, 23% miscarriages and 15% therapeutic abortions. A third of patients had fewer children than desired due to disease activity and medications. Notably, no statistically significant differences occurred between pregnancies before or after RA/PsA diagnosis regarding pregnancy planning, fertility treatment, pregnancy and delivery complications, birth defect frequency or neonatal complications (Dissanayake et al., 2020).

Larger studies, mainly from US registries, showed an increased rate of some complications such as preterm delivery and IUGR that appeared to be related to the active disease during pregnancy. The pathogenic mechanism that allows increased disease activity to cause these complications is not certain yet, although inflammation could be a possible explanation (Littlejohn, 2020).

Malformations

As previously detailed, according to the available international guidelines, treatment with TNF inhibitors can be offered to pregnant patients. Because of their protein nature, these large molecules (mainly IgG derived) cannot reach the embryo in the first trimester, the critical period for organogenesis, while they can actively reach the fetus in the third trimester, with the possible increased risk of neonatal infections. Most of the data about the risk of malformations in patients with inflammatory arthritis come from the registries.

Recently a nationwide registry-based study including all male live births from RA and SLE in Denmark from 1995 to 2016 was published with the aim to assess the occurrence of cryptorchidism and hypospadias (the most frequent malformations in boys) according to the prenatal disease-state of the mothers. They found among 690,240 boys, 1,026 born from mother with RA and 352 from mothers with SLE. Compared with unexposed boys, these subgroups of children had a higher risk of cryptorchidism: Authors described an adjusted hazard ratio of 1.72 (95% CI: 1.15; 2.57) in the group of RA-children and 1.46 (95% CI: 0.69; 3.06) in the SLE-group. No conclusion could be reached on the risk of hypospadias, due to the low number of events (Knudsen et al., 2020a).

Another recent retrospective cohort study displays similar results: congenital anomalies, small for gestational age and preterm birth were more common in neonates of women with RA compared with controls (Aljary et al., 2020). Unfortunately, data about medication employed both before and during the pregnancy (type, dosage, duration of use) were not available.

Newborns Infections

One of the main concerns about biological treatment during pregnancy, considering the mechanism of action, is the possible increased risk of infections in newborns. Follow-up studies of anti-TNFα therapy during pregnancy and the risk of infections in the offspring were firstly conducted in women with IBD. IFX and ADA have been detected in the infants' circulation and may remain detectable up to 6–12 months of life (Julsgaard et al., 2016), while CTZ was not found in neonates (Mariette et al., 2018) and in maternal milk (Clowse et al., 2017).

A recent multicenter study with a mean follow-up of 4 years reported no increase in hospital admission for infections in children born to women with IBD who had been treated at any time during pregnancy or during the 3 months before conception with anti-TNFα compared with women with IBD without anti-TNFα therapy (Chaparro et al., 2018). Similar results were described in a French study that reported no increased risk of pediatric infections in a large cohort of children born to women with IBD treated with anti-TNFα during pregnancy (Luu et al., 2018).

A Canadian study by Vinet et al. evaluated 2,989 children born to women with RA exposed to anti-TNFα during pregnancy, including exposure in the third trimester: the Authors could not detect a significant increased risk for serious infections (Vinet et al., 2018).

On the other hand, Juulsgaard et al. reported that the risk of infection was significantly increased in a cohort of 80 women with IBD treated with ADA or IFX (Julsgaard et al., 2016).

Recently a three-country population-based cohort (Denmark, Sweden, and Finland) was published. Aim of the work was to described the risks of hospital admissions for infection in a cohort of children born to women treated with anti-TNFα during pregnancy compared to women with the same diseases, but not treated during pregnancy, and healthy controls. Data were recorded from the national medical birth registries, patients' registries and prescribed drug registries. 1,617,886 children were included: 1,027 were born to treated women and 9,346 to women with non-biologic systemic treatment. The results showed an increased rate of hospital admissions due to infections in the first year of life, as well as increased rates for antibiotic prescriptions during the second year of life. There was no differences among different anti-TNFα, and there was no distinct pattern for type of infection (Bröms et al., 2020).

Vaccinations

Finally, we report some data regarding the response to vaccinations of children and its safety. There are some controversial data to the safety of live vaccines administered in early childhood to the children of mothers exposed to anti-TNFα during pregnancy, but the data are non-conclusive. European and North American guidelines for patients with IBD recommend postponing the use of live vaccines until 6 months post-delivery (Nguyen et al., 2016).

There is at least one reported fatality case due to disseminated tuberculosis infection in an infant who received a Bacillus Calmette-Guerin for tuberculosis (BCG) vaccination at 3 months of age and whose mother had been taking IFX 10 mg/kg every 8 weeks for Crohn's disease during all the pregnancy (Cheent et al., 2010; Heller et al., 2011). Recently a French nationwide population-based cohort on the safety of vaccinations during the first year of life in exposed children was published (Luu et al., 2019). The Authors studied 670 children exposed to anti-TNFα during pregnancy of women with IBD: among these exposed children, 88 (13%) received BCG live vaccine before 6 months of life and no adverse events were reported. To note, for the great part of the mothers (61.5%) the time for last exposure to anti-TNFα therapy was ≥26 weeks of gestation.

A recent study in children born to mothers with IBD and exposed to anti-TNFα *in utero* (IFX and ADA) showed adequate immune serologic response for Hepatitis B vaccination compared to children not exposed. The median anti-TNFα stop week was 25 (IQR 22–29) in the IFX group and gestational week 23 (IQR 22–24) in the ADA group. There are no differences between the groups also in birth outcome (de Lima et al., 2018).

All these data came from IBD mothers that mainly received anti-TNFα therapy during all the course of pregnancy, but we can assume that data could be analogous in women with inflammatory arthritis who usually receive therapy until the 32–34th week of gestation.

THE LONG-TERM OUTCOME OF CHILDREN BORN TO WOMEN WITH INFLAMMATORY ARTHRITIS

The long-term outcome of children represents a remarkably interesting area, certainly challenging the investigators.

Epigenetic

One of the hypotheses is that some adverse event occurring in pregnancy could cause long-term consequences. Pathological alteration of pregnancy could also act "*via*" epigenetic changes in children themselves possibly are involved in long-term consequences (Jones et al., 2019). In this respect, DNA methylation profile of children born to RA mothers was recently investigated. This is a well-studied fetal epigenetic modification, that, in this case, was demonstrated to be related with several risk factors (maternal disease, malnutrition, smoking, placental insufficiency, corticosteroids, folate depletion and cytokines). Samples from 80 children were analyzed (mean age 6.4 years old) from RA mothers and 354 controls. They found some differences between the DNA methylation in the two groups, and, notably, some of the differentially methylated sequences or their nearby genes were associated with cardiovascular or metabolic disease. It can be speculated that DNA methylation could influence the long-term outcome of these children and open new interesting scenarios. It remains unknown whether the identified associations are causal, and if so, whether they are caused by either the disease or the treatment during pregnancy (Ince-Askan et al., 2019b).

Maternal Condition in Puerperium

Maternal disease state after delivery could also influence the long-term outcome of the children. Smeele et al. recently investigated women affected by rheumatoid arthritis. In their work, high Health Assessment Questionnaire (HAQ) scores in the first trimester, high disease activity in the first trimester, disease duration and the presence of erosive disease were predictive for developing parenting disability after delivery. Unfortunately, whether mothers' disabilities could affect the children was not investigated (Smeele et al., 2020).

Autoimmune Disease, Congenital Heart Defect and Neurodevelopmental Disorders

A 2017 a review focused on the long-term outcome of children born to women affected by RA and Systemic Lupus Erythematosus. As previously reported, these data were also derived by national registries, with all the limitations related to this data collection. The authors concluded that these children could be potentially at increased risk of neurodevelopmental disorders, congenital heart defects and autoimmune diseases, compared with children from the general population. Genetic factors, obstetric complications, maternal autoantibodies, cytokines and drugs might be related to the increased risk. However, the extremely low rate of these events is overall reassuring: the absolute risk is small, and patients should not be discouraged from having children (Vinet and Bernatsky, 2017).

Autism

A possible relationship between RA in mothers and autism spectrum disorders were hypothesized. In a systematic literature review, 70 articles on this topic were included. A potentially increased risk of developing autism in children born to mothers with RA was described, although data are limited and conclusions not definitive (Wojcik et al., 2017).

School Achievement

School performance can be considered a good indicator of a possible cognitive impairment and it was investigated in children born to mothers with chronic arthritis. In fact, a recent Danish study examined the overall cognitive development of children born from RA mothers by comparing their school test scores with those of their peers. They linked data from the National School Test Register and national registries of disease and evaluated about 1,000 children. There were no differences between the groups in reading test scores while RA exposed children scored poorer in mathematics tests. Furthermore, there was no appreciable difference in children exposed to maternal seropositive RA or between children exposed to preclinical RA versus children exposed to established RA. To note, no relationship with therapy was described, probably due to missing data (Knudsen et al., 2020b).

OUR EXPERIENCE: THE NEUROPSYCHOLOGICAL OUTCOME OF SCHOOL-AGE CHILDREN BORN TO WOMEN WITH INFLAMMATORY ARTHRITIS

As far as we know, no studies have described the neuropsychological status of children born to mothers with RA by means of validated questionnaires and direct neurological physical examination.

In our Hospital, a multidisciplinary team (rheumatologists and child neuropsychiatrists) has carried out a study to evaluate the school performance and the psychological profile of a group of children born to mothers with chronic arthritis. The study included 16 women (11 RA, 3 PsA, 2 ankylosing spondylitis - SpA) with the diagnosis before pregnancy and their 18 school-age children (F/M = 1/1, median age 8 years, range 6–14). Information about maternal disease and treatment during pregnancy were collected from medical records (pregnancies had been prospectively followed-up in our Pregnancy Clinic). Three validated questionnaires were administered to all the mothers at the time of the children follow-up: the Child Behavior Check List (CBCL 6–18; Achenbach and Rescorla, 2001), a screening tool, used to identify clinical, borderline and normative behaviors in the children; the State-Trait Anxiety Inventory (STAI; Spielberg et al., 1970) to measure trait and state anxiety of the mothers during all their life and at the time

TABLE 2 | The personality profile of children according to maternal disease characteristics.

Maternal characteristics	Child personality (*n* = 18)		*p* value
	Not at risk of neuro-developmental problems (*n* = 7)	At risk of neuro-developmental problems (*n* = 11)	
Disease duration at conception (median years; IQR)	2 (2; 5)	10 (7.5; 13)	**<0.05**
Active disease during pregnancy (*n*, %)	1 (14%)	6 (55%)	ns
Active disease in the post-partum period (*n*, %)	5 (71%)	8 (73%)	ns
Severe disease activity in the post-partum period (*n*, %)	3 (43%)	8 (73%)	ns
Positive antiphosholipid antibodies (*n*, %)	2 (29%)	2 (18%)	ns
Positive rheumatoid factor (*n*, %)	2 (29%)	3 (27%)	ns
Positive anti-citrullinated peptides (*n*, %)	0 (0%)	1 (9%)	ns
Employment (*n*, %)	7 (100%)	7 (64%)	ns
Positive EPDS questionnaire (depression) (*n*, %)	2 (29%)	5 (45%)	ns
Post-partum depression reported by mothers (*n*, %)	2 (29%)	5 (45%)	ns
Positive STAI questionnaire (anxiety) (*n*, %)	2 (29%)	6 (55%)	ns
Anxiety reported by mothers (*n*, %)	3 (43%)	5 (45%)	ns
Psychological support received during the post-partum period (*n*, %)	1 (14%)	4 (36%)	ns
Difficulty in caregiving, as rated by the patient (*n*, %)	3 (43%)	6 (55%)	ns
Duration of Breastfeeding (months median, IQR)	6 (6, 8.5)	1 (0; 4.5)	<0.05
Breastfeeding for less than 6 months (*n*, %)	1 (14%)	9 (82%)	<0.05
STOP Breastfeeding because of the need of taking drugs (*n*, %)	3 (43%)	5 (45%)	ns

Abbreviations: EPDS, Edinburgh Postnatal Depression Scale; IQR, interquartile range; ns, not significant; STAI, State-Trait Anxiety Inventory.

of their child evaluation; and the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) to identify mothers who may have postpartum depression; in our work this was a retrospective evaluation with possible bias, even if a vivid memory of the post-natal period was reported by all the mothers.

Notably, according to the clinical reports, at the time of the interview, maternal disease was effectively treated and all the patients were found in clinical remission.

A child neuropsychiatrist performed a neurological physical examination of all the children. In addition, the Wechsler Intelligence Scale for Children-IV (Wechsler, 2003) to evaluate cognitive level was administered to all the children; this instrument provides a Full Scale Intelligence Quotient and four Composite or Index Scores (Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed Index). Finally, standardized batteries of tests to evaluate academic learning (Test AC-MT 6-11, 2002; Cornoldi and Cazzola, 2003; Sartori et al., 2007; Cornoldi and Carretti, 2016) were also administered. We evaluated speed and accuracy of text reading (MT-3 test, 56) and, only for children scored greater than the Dyslex-ia spectrum cut-off, the speed and accuracy of words and nonsense words reading (DDE-2 test, items 2 and 3,57) were also evaluated. Words and nonsense words writing (DDE-2, items 6 and 7, 57) were measured as well as the arithmetic abilities (Test AC-MT 6-11, 2002; Cornoldi and Cazzola, 2003). The neurological physical examination and the intelligence quotient were normal in all the children as well as the academic skills.

According to CBCL questionnaire, behavioral aspects of somatization and anxiety/depression (internalizing problem) were found in six children (33%) and an "adult profile" in 5 (28%). We also found that all children were less involved in sports or playing activities than peers but more involved in school activities, as they seemed to invest more energies in intellectual functioning.

We searched for associations between the risk of behavioral difficulties in children and the maternal characteristics (**Table 2**).

Our results seem to show that children at high-risk of behavioral problems were born to mothers with a longer history of arthritis and were breastfed for less than 6 months of age or were not breastfed at all (see **Table 2**). No association was found with other maternal characteristics such as autoantibody presence and disease activity during and after pregnancy.

On the maternal side, according to STAI questionnaire, we identified seven mothers (44%) with a state of anxiety both at the time of the study and during the all life.

The results from EPDS were quite similar reported a significant score for the risk of post-partum depression.

We found significant associations between active disease during pregnancy and difficulties in caregiving and breastfeeding ($p = 0.005$ and $p = 0.0128$, respectively). In addition, only twelve mothers breastfed their children (67%). The patients recollected a diffuse state of anxiety mainly due to their active disease as a major obstacle toward a normal parenting experience.

This study has several limitations: 1) the number of examined children is small; 2) maternal disease data are retrospective and based on clinical records; 3) the psychological evaluation of the mothers was performed only in a single time-point at the time of the interview and a serial evaluation of their psychological status was not available.

However, it has also the strength of an original investigation about the risk of cognitive and behavioral problems of children born to mother with inflammatory arthritis. These data are in line with our previous preliminary study (Bomba et al., 2010) already supporting the hypothesis that the mother's disease impaired

child handling and care-taking in the first years of life interfering with the parenthood and baby holding, impacting on maternal-fetal attachment and on the children development.

Even taking into account the above quoted limitations, our study suggests that children born to women with chronic arthritis are normal from a neurological, cognitive and learning point of view. However, they may display behavioral difficulties, that we found related to a complicated maternal experience during pregnancy and the post-partum period, even if it cannot be excluded the influence of maternal chronic disease long-life (Bomba et al., 2010). Therefore, it could be reasonable to assess closely the psychological status of patients during pregnancy and after delivery, along with the activity of the rheumatic disease. The prompt management of an eventually occurring post-partum depression could be of great help to both the mother and the baby and possibly prevent the behavioral problems observed later on. In addition, if a child displays any difficulty during school years, the mother should be encouraged to refer to specialists and be reassured that the early diagnosis yields the best outcomes for the child.

CONCLUSION

In women suffering from inflammatory arthritis, the importance of preconception counselling, of the treatment and of the follow up during pregnancy is today well recognized because active disease can be responsible for the increased risk of preterm delivery and intrauterine growth restriction.

If we exclude methotrexate, conventional anti-rheumatic drugs and TNF-inhibitors used in the treatment of patients with inflammatory arthritis can be prescribed during pregnancy and are not linked to an increased risk of malformations although minor malformations associated to maternal RA have been reported (Götestam Skorpen et al., 2016; Knudsen et al., 2020a; Sammaritano et al., 2020).

The transient immunosuppression possibly occurring in some neonates exposed to new biological drugs, does not seem to be of great clinical relevance. However, according to the current recommendations, live vaccines should be avoided in the first 6 months of life.

Despite these recent achievements, patients are often afraid of taking drugs during pregnancy. Certainly, information about the long-term outcome of children exposed *in utero* can increase their compliance and confidence to the prescribed treatment.

The overall occurrence of autoimmune disease, heart congenital defects and neurodevelopmental problems seem rare, although autism disorders were reported. Children of mothers affected by RA seem to have some difficulties in mathematic tests, but not in reading or writing. These data were derived by the results of school tests and no information on maternal treatment was available. Most importantly, none of these children was directly examined.

The direct neurological examination of a small cohort of school age children from patients affected by inflammatory arthritis allowed us to highlight some minor behavioral alterations related to anxiety/depression often yielding an "adult profile." The affected children performed better in schoolwork than in social/physical activities, possibly reflecting the maternal limitations in everyday life. The drug regimens during pregnancy were not related to the occurrence of these problems. Rather, the disease activity during pregnancy and puerperium, and the lack of breastfeeding seems to play an important role in the onset of behavioral problems. Therefore, our data can suggest that a safe and effective treatment of maternal disease during pregnancy and puerperium is needed to ensure not only a good pregnancy outcome but also a physiological development of the children.

AUTHOR CONTRIBUTIONS

The rheumatology group (CN, DL, SP, ML, LA, FF, and AT) equally contributed to the literature search. LA, FF, and AT contributed to the final revision of the work with YS. CN with the child neurologists (JG, AMe, and EF) contributed to the evaluation of children and their mothers. Gynecologists (SZ, VB, JK, and AMa) helped reviewing the work.

REFERENCES

Achenbach, T. M., and Rescorla, L. A. (2001). *Manual for the ASEBA school-age forms and profiles*. Burlington, Canada: University of Vermont, Research Center for Children, Youth, and Families.

Ahmed, K., Giles, I., Nguyen, H., and Flint, J. (2020). A systematic review of the safety of non-tumour necrosis factor inhibitor and targeted synthetic drugs in rheumatic disease in pregnancy. *Clin. Med.* 20 (2), s98. doi:10.7861/clinmed.20-2-s98

Aljary, H., Czuzoj-Shulman, N., Spence, A. R., and Abenhaim, H. A. (2020). Pregnancy outcomes in women with rheumatoid arthritis: a retrospective population-based cohort study. *J. Matern. Fetal Neonatal. Med.* 33 (4), 618–624. doi:10.1080/14767058.2018.1498835

Andreoli, L., Lazzaroni, M. G., Carini, C., Dall'Ara, F., Nalli, C., Reggia, R., et al. (2019). "Disease knowledge index" and perspectives on reproductive issues: a nationwide study on 398 women with autoimmune rheumatic diseases. *Joint Bone Spine* 86 (4), 475–481. doi:10.1016/j.jbspin.2018.12.002

Atta, D. S., Girbash, E. F., Tharwat, I., Abdelwahab, S. M., Abdeldayem, H. M., and Ghonaim, R. (2016). Maternal cytokines and disease severity influence pregnancy outcomes in women with rheumatoid arthritis. *J. Matern. Fetal Neonatal. Med.* 29, 3358–3363. doi:10.3109/14767058.2015.1127342

Bomba, M., Galli, J., Nacinovich, R., Ceribelli, A., Motta, M., Lojacono, A., et al. (2010). Neuropsychiatric aid in children born to patients with rheumatic diseases. *Clin. Exp. Rheumatol.* 28 (5), 767–773.

Borba, V. V., Zandman-Goddard, G., and Shoenfeld, Y. (2019). Exacerbations of autoimmune diseases during pregnancy and postpartum. *Best Pract. Res. Clin. Endocrinol. Metab.* 33 (6), 101321. doi:10.1016/j.beem.2019.101321

Bortoluzzi, A., Andreoli, L., Carrara, G., Ramoni, V., Rumi, F., Padovan, M., et al.RECORD study of the Italian Society for Rheumatology (2021). Improved pregnancy outcome in patients with rheumatoid arthritis who followed an ideal clinical pathway. *Arthritis Care Res.* 73, 166–172. doi:10.1002/acr.24116

Bröms, G., Kieler, H., Ekbom, A., Mika, G., Karin, H., Maarit, K. L., et al. (2020). Paediatric infections in the first 3 years of life after maternal anti-TNF treatment during pregnancy. *Aliment. Pharmacol. Ther.* 52, 843–854. doi:10.1111/apt.15971

Chaparro, M., Verreth, A., Lobaton, T., Gravito-Soares, E., Julsgaard, M., Savarino, E., et al. (2018). Long-term safety of *in utero* exposure to anti-TNFα drugs for the treatment of inflammatory bowel disease: results from the multicenter European TEDDY study. *Am. J. Gastroenterol.* 113 (3), 396–403. doi:10.1038/ajg.2017.501

Cheent, K., Nolan, J., Shariq, S., Kiho, L., Pal, A., and Arnold, J. (2010). Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J. Crohns Colitis* 4, 603–605. doi:10.1016/j.crohns.2010.05.001

Chew, C., Rebić, N., Baldwin, C., Amiri, N., Proulx, L., and De Vera, M. A. (2019). "r/Thritis", pregnancy, and parenting: a qualitative descriptive study of Reddit forums to explore information needs and concerns of women with rheumatoid arthritis. *ACR Open Rheumatol.* 1 (8), 485–492. doi:10.1002/acr2.11069

Clowse, M. E. B., Förger, F., Hwang, C., Thorp, J., Dolhain, R. J., van Tubergen, A., et al. (2017). Minimal to no transfer of certolizumab pegol into breast milk: results from CRADLE, a prospective, postmarketing, multicentre, pharmacokinetic study. *Ann. Rheum. Dis.* 76 (11), 1890–1896. doi:10.1136/annrheumdis-2017-211384

Clowse, M. E. B., Scheuerle, A. E., Chambers, C., Afzali, A., Kimball, A. B., Cush, J. J., et al. (2018). Pregnancy outcomes after exposure to certolizumab pegol: updated results from a pharmacovigilance safety database. *Arthritis Rheumatol.* 70 (9), 1399–1407. doi:10.1002/art.40508

Cornoldi, C., and Carretti, B. (2016). *Prove MT-3-clinica -la valutazione delle abilità di lettura e comprensione per la scuola primaria e secondaria di° grado*. Firenze, Italy: Giunti EDU.

Cornoldi, C., and Cazzola, C. (2003). *Test di valutazione delle abilità di calcolo e problem solving dagli 11 ai 14 anni*. Trento, Italy; Erickson.

Cox, J. L., Holden, J. M., and Sagovsky, R. (1987). Detection of postnatal depression. Development of the 10–item Edinburgh Postnatal Depression Scale. *Br. J. Psychiatry* 150, 782–786. doi:10.1192/bjp.150.6.782

de Lima, A., Kanis, S. L., Escher, J. C., and van der Woude, C. J. (2018). Hepatitis B vaccination effective in children exposed to anti-tumour necrosis factor alpha *in utero*. *J. Crohns Colitis* 12 (8), 948–953. doi:10.1093/ecco-jcc/jjy053

Dissanayake, T. D., Maksymowych, W. P., and Keeling, S. O. (2020). Peripartum issues in the inflammatory arthritis patient: a survey of the RAPPORT registry. *Sci. Rep.* 10 (1), 3733. doi:10.1038/s41598-020-60451-2

Eudy, A. M., McDaniel, G., and Clowse, M. E. B. (2018). Pregnancy in rheumatoid arthritis: a retrospective study. *Clin. Rheumatol.* 37 (3), 789–794. doi:10.1007/s10067-017-3939-4

Flint, J., Panchal, S., Hurrell, A., van de Venne, M., Gayed, M., Schreiber, K., et al. (2016a). BSR and BHPR standards, guidelines and audit working group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. *Rheumatology* 55 (9), 1693–1697. doi:10.1093/rheumatology/kev404

Flint, J., Panchal, S., Hurrell, A., van de Venne, M., Gayed, M., Schreiber, K., et al. (2016b). BSR and BHPR standards, guidelines and audit working group. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part II: analgesics and other drugs used in rheumatology practice. *Rheumatology* 55 (9), 1698–1702. doi:10.1093/rheumatology/kev405

Furer, V., Rondaan, C., Heijstek, M. W., Agmon-Levin, N., van Assen, S., Bijl, M., et al. (2020). 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann. Rheum. Dis.* 79 (1), 39–52. doi:10.1136/annrheumdis-2019-215882

Ghalandar, N., Dolhain, R. J. E. M., Hazes, J. M. W., Siezen, C. L. E., van der Laan, J. W., Crijns, H. J. M. J., et al. (2020). The pre- and post-authorisation data published by the European medicines agency on the use of biologics during pregnancy and lactation. *Br. J. Clin. Pharmacol.* 86 (3), 580–590. doi:10.1111/bcp.14145

Giles, I., Yee, C. S., and Gordon, C. (2019). Stratifying management of rheumatic disease for pregnancy and breastfeeding. *Nat. Rev. Rheumatol.* 15 (7), 391–402. doi:10.1038/s41584-019-0240-8

Götestam Skorpen, C., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., et al. (2016). The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann. Rheum. Dis.* 75 (5), 795–810. doi:10.1136/annrheumdis-2015-208840

Heller, M. M., Wu, J. J., and Murase, J. E. (2011). Fatal case of disseminated BCG infection after vaccination of an infant with *in utero* exposure to infliximab. *J. Am. Acad. Dermatol.* 65 (4), 870. doi:10.1016/j.jaad.2011.04.030

Ince-Askan, H., Hazes, J. M. W., and Dolhain, R. J. E. M. (2019a). Breastfeeding among women with rheumatoid arthritis compared with the general population: results from a nationwide prospective cohort study. *J. Rheumatol.* 46 (9), 1067–1074. doi:10.3899/jrheum.180805

Ince-Askan, H., Mandaviya, P. R., Felix, J. F., Duijts, L., van Meurs, J. B., Hazes, J. M. W., et al. (2019b). Altered DNA methylation in children born to mothers with rheumatoid arthritis during pregnancy. *Ann. Rheum. Dis.* 78 (9), 1198–1204. doi:10.1136/annrheumdis-2018-214930

Jethwa, H., Lam, S., Smith, C., and Giles, I. (2019). Does rheumatoid arthritis really improve during pregnancy? A systematic review and metaanalysis. *J. Rheumatol.* 46 (3), 245–250. doi:10.3899/jrheum.180226

Jones, H. J., Hubbard, L., Mitchell, R. E., Jones, S. A., Williams, N. M., Zammit, S., et al. (2019). Association of genetic risk for rheumatoid arthritis with cognitive and psychiatric phenotypes across childhood and adolescence. *JAMA Netw. Open* 2 (6), e196118. doi:10.1001/jamanetworkopen.2019.6118

Julsgaard, M., Christensen, L. A., Gibson, P. R., Gearry, R. B., Fallingborg, J., Hvas, C. L., et al. (2016). Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology* 151 (1), 110–119. doi:10.1053/j.gastro.2016.04.002

Knudsen, S. S., Bech, B. H., Deleuran, B. W., Ramlau-Hansen, C. H., and Arendt, L. H. (2020a). Maternal rheumatoid arthritis and systemic lupus erythematosus and risk of cryptorchidism and hypospadias in boys: a Danish nationwide study. *Rheumatology (Oxford)* 59 (8), 1871–1877. doi:10.1093/rheumatology/kez538

Knudsen, S. S., Simard, J. F., Christensen, J., Laursen, T. M., Deleuran, B. W., and Bech, B. H. (2020b). Rheumatoid arthritis in pregnancy and school performance in offspring. *Arthritis Care Res.* doi:10.1002/acr.24223

Littlejohn, E. A. (2020). Pregnancy and rheumatoid arthritis. *Best Pract. Res. Clin. Obstet. Gynaecol.* 64, 52–58. doi:10.1016/j.bpobgyn.2019.09.005

Luu, M., Benzenine, E., Barkun, A., Doret, M., Michiels, C., Degand, T., et al. (2019). Safety of first year vaccination in children born to mothers with inflammatory bowel disease and exposed *in utero* to anti-TNFα agents: a French nationwide population-based cohort. *Aliment. Pharmacol. Ther.* 50 (11–12), 1181–1188. doi:10.1111/apt.15504

Luu, M., Benzenine, E., Doret, M., Michiels, C., Barkun, A., Degand, T., et al. (2018). Continuous anti-TNFα use throughout pregnancy: possible complications for the mother but not for the fetus. A retrospective cohort on the French national health insurance database (EVASION). *Am. J. Gastroenterol.* 113 (11), 1669–1677. doi:10.1038/s41395-018-0176-7

Mariette, X., Förger, F., Abraham, B., Flynn, A. D., Moltó, A., Flipo, R. M., et al. (2018). Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study. *Ann. Rheum. Dis.* 77 (2), 228–233. doi:10.1136/annrheumdis-2017-212196

Nguyen, G. C., Seow, C. H., Maxwell, C., Huang, V., Leung, Y., Jones, J., et al.IBD in Pregnancy Consensus Group; Canadian Association of Gastroenterology (2016). The Toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology* 150 (3), 734–757. doi:10.1053/j.gastro.2015.12.003

Østensen, M. (2004). New insights into sexual functioning and fertility in rheumatic diseases. *Best Pract. Res. Clin. Rheumatol.* 18 (2), 219–232. doi:10.1016/j.berh.2004.01.002

Østensen, M. (2017a). Preconception counseling. *Rheum. Dis. Clin. N. Am.* 43 (2), 189–199. doi:10.1016/j.rdc.2016.12.003

Østensen, M. (2017b). Sexual and reproductive health in rheumatic disease. *Nat. Rev. Rheumatol.* 13 (8), 485–493. doi:10.1038/nrrheum.2017.102

Østensen, M., Aune, B., and Husby, G. (1983). Effect of pregnancy and hormonal changes on the activity of rheumatoid arthritis. *Scand. J. Rheumatol.* 12 (2), 69–72. doi:10.3109/03009748309102886

Østensen, M., Förger, F., Nelson, J. L., Schuhmacher, A., Hebisch, G., and Villiger, P. M. (2005). Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann. Rheum. Dis.* 64 (6), 839–844. doi:10.1136/ard.2004.029538

Sammaritano, L. R., Bermas, B. L., Chakravarty, E. E., Chambers, C., Clowse, M. E. B., Lockshin, M. D., et al. (2020). 2020 American college of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol.* 72 (4), 529–556. doi:10.1002/art.41191

Sartori, G., Job, R., and Tressoldi, P. (2007). *Batteria per la valutazine della displessia e della disortografia evolutiva-2*. Firenze, Italy: Organizzazioni Speciali.

Sinclair, S., Cunnington, M., Messenheimer, J., Weil, J., Cragan, J., Lowensohn, R., et al. (2014). Advantages and problems with pregnancy registries: observations and surprises throughout the life of the International Lamotrigine Pregnancy Registry. *Pharmacoepidemiol. Drug Saf.* 23 (8), 779–786. doi:10.1002/pds.3659

Smeele, H. T. W., de Man, Y. A., Röder, E., Wintjes, H., Hazes, J. M. W., and Dolhain, R. J. E. M. (2020). Parenting problems postpartum can be detected early in pregnancy in patients with rheumatoid arthritis. *RMD Open* 6 (2), e001276. doi:10.1136/rmdopen-2020-001276

Spielberg, C. D., Gorusch, R. L., and Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologist Press.

Test AC-MT 6-11 (2002). *di valutazione delle abilità di calcolo*. Trento, Italy: Erickson.

Tsao, N. W., Rebic, N., Lynd, L. D., and De Vera, M. A. (2020). Maternal and neonatal outcomes associated with biologic exposure before and during pregnancy in women with inflammatory systemic diseases: a systematic review and meta-analysis of observational studies. *Rheumatology (Oxford)* 59 (8), 1808–1817. doi:10.1093/rheumatology/keaa064

Van den Brandt, S., Zbinden, A., Baeten, D., Villiger, P. M., Østensen, M., and Förger, F. (2017). Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. *Arthritis Res. Ther.* 19, 64. doi:10.1186/s13075-017-1269-1

Vieira Borba, V., and Shoenfeld, Y. (2019). Prolactin, autoimmunity, and motherhood: when should women avoid breastfeeding? *Clin. Rheumatol.* 38 (5), 1263–1270. doi:10.1007/s10067-018-04415-y

Vinet, É., and Bernatsky, S. (2017). Outcomes in children born to women with rheumatic diseases. *Rheum. Dis. Clin. N. Am.* 43 (2), 263–273. doi:10.1016/j.rdc.2016.12.006

Vinet, É., De Moura, C., Pineau, C. A., Abrahamowicz, M., Curtis, J. R., and Bernatsky, S. (2018). Serious infections in rheumatoid arthritis offspring exposed to tumor necrosis factor inhibitors: a cohort study. *Arthritis Rheumatol.* 70 (10), 1565–1571. doi:10.1002/art.40536

Wechsler, D. W. (2003). *Wechsler intelligence scale for children–fourth edition administration and scoring manual*. San Antonio, TX: Pearson.

Wojcik, S., Bernatsky, S., Platt, R. W., Pineau, C. A., Clarke, A. E., Fombonne, É., et al. (2017). Risk of autism spectrum disorders in children born to mothers with rheumatoid arthritis: a systematic literature review. *Arthritis Care Res.* 69 (12), 1926–1931. doi:10.1002/acr.23235

Wood, H., Acharjee, A., Pearce, H., Quraishi, M., Powell, R., Rossiter, A., et al. (2020). Breastfeeding promotes early neonatal regulatory T cell expansion and immune tolerance of non-inherited maternal antigens. *Authorea*. doi:10.22541/au.160199734.46067798/v1

Zbinden, A., Brandt, S., Østensen, M., Villiger, P. M., and Förger, F. (2018). Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis: disease activity matters. *Rheumatology* 57, 1235–1242. doi:10.1093/rheumatology/key053

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor declared a past co. authorship with several of the authors CN, LA, FF, AT, SP, and MGL.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 16 April 2021
doi: 10.3389/fphar.2021.660123

SLE-DAS in the First Trimester of Gestation Predicts Maternal Lupus Flares Later in Pregnancy

*Maddalena Larosa[1,2,3], Nathalie Costedoat-Chalumeau[2,3,4], Gaëlle Guettrot-Imbert[2,3], Veronique Le Guern[2,3], Nathalie Morel[2,3], Diogo Jesus[5,6], Luca Iaccarino[1], Luís Inês[5,7] and Andrea Doria[1]**

[1]Rheumatology Unit, Department of Medicine, DIMED, University of Padova, Padova, Italy, [2]Internal Medicine Department, Hôpital Cochin, Paris, France, [3]Centre de Référence Maladies Auto-immunes et Systémiques Rares, Paris, France, [4]University of Paris, Paris, France, [5]Faculty of Health Sciences, University of Beira Interior, Covilhã, Portugal, [6]Rheumatology Department, Centro Hospitalar de Leiria, Leiria, Portugal, [7]Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Introduction: Systemic Lupus Erythematosus (SLE) mainly occurs during childbearing age. Remission or low disease activity state (LDAS) before conception are recommended by experts to achieve a favourable lupus pregnancy outcome but little is known on the best way to evaluate remission or activity status during pregnancy.

Objectives: We tested SLE-disease activity score (SLE-DAS) in the first trimester as predictor of maternal flares and obstetrical complications in 2nd and 3rd trimester in a cohort of SLE pregnant women.

Patients and Methods: Inclusion criteria were: 1) women ≥ 18 years; 2) affected with SLE (SLICC 2012); 3) enrolled in two referral centers (Italy and France) 4) with an ongoing singleton pregnancy at 12 weeks (only one pregnancy per patient). Disease activity was assessed at first trimester of pregnancy, using SLE-pregnancy disease activity index (SLEPDAI) and retrospectively applying SLE-DAS. Maternal lupus flares at 2nd and 3rd trimester were defined by the SELENA-SLEDAI Flare Index (SFI). Adverse pregnancy outcome (APO) included: fetal and neonatal death, placental insufficiency with premature delivery <37 weeks, and small for gestational age (SGA) (≤3rd percentile).

Results: We included 158 pregnant patients affected with SLE. At first trimester the median SLEPDAI (IQR) was 2 (0–4) and the median SLE-DAS (IQR) 1.32 (0.37–2.08). At least one flare occurred in 25 (15.8%) women during the 2nd and 3rd trimester. APO occurred in 19 (12.0%) patients. A significant correlation between SLE-DAS and SLEPDAI was found in this cohort (Spearman's ρ = 0.97, **Figure 1**). At multivariate analysis, both SLE-DAS and SLEPDAI predicted maternal flares (adjOR = 1.2; 95% CI = 1.0–1.3, p = 0.02; adjOR 1.3, 95% CI = 1.1–1.6 per unit increase, p = 0.01, respectively). SLE-DAS and SLEPDAI were associated with APO at univariate analysis (p = 0.02).

Conclusions: SLE-DAS was highly correlated with SLEPDAI and its use in the first trimester predicted maternal flares in the 2nd and 3rd trimester, making SLE-DAS a reliable instrument to measure SLE activity during pregnancy.

Keywords: systemic lupus erythematosus, SLE-DAS, pregnancy, maternal flares, adverse obstetrical outcome

OPEN ACCESS

Edited by:
Maria Gerosa,
University of Milan, Italy

Reviewed by:
Giacomo Emmi,
Università degli Studi di Firenze, Italy
Ashwin Karanam,
Pfizer (United States), United States

****Correspondence:***
Andrea Doria
adoria@unipd.it

Specialty section:
This article was submitted to Obstetric and Pediatric Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *28 January 2021*
Accepted: *18 March 2021*
Published: *16 April 2021*

Citation:
Larosa M, Costedoat-Chalumeau N, Guettrot-Imbert G, Le Guern V, Morel N, Jesus D, Iaccarino L, Inês L and Doria A (2021) SLE-DAS in the First Trimester of Gestation Predicts Maternal Lupus Flares Later in Pregnancy. Front. Pharmacol. 12:660123. doi: 10.3389/fphar.2021.660123

INTRODUCTION

It is well known that Systemic Lupus Erythematosus (SLE) mainly affects women in childbearing age, with a ratio of female-to-male close to 9:1 (Pons-Estel et al., 2017). Therefore, pregnancy is common in SLE patients, who are at risk for complications such as maternal flares, preeclampsia (PE), foetal loss, and preterm birth (Larosa et al., 2019).

During the last few decades, the outcome of pregnancy in SLE has consistently improved, possibly due to preconception counseling (Andreoli et al., 2017). Risk stratification before conception is pivotal to achieve a favourable outcome (Andreoli et al., 2017) and it should assess SLE remission, autoantibodies (Abs) profile, treatment and previous pregnancy morbidity (Andreoli et al., 2017). Indeed, active/flaring SLE in the 6–12 months before conception is a major risk factor for flares during pregnancy and/or puerperium, as well as for foetal morbidity (i.e. intra-uterine growth restriction-IUGR-, pregnancy loss and preterm delivery) (Andreoli et al., 2017).

In the past decades, efforts has been made to prevent damage accrual in SLE patients by developing treat-to-target (T2T) strategies (Gatto et al., 2019; Jesus et al., 2019a) which primarily pursue the achievement of a durable remission or at least a low disease activity state (LDAS) (Zen et al., 2015; Franklyn et al., 2016; Fischer-Betz and Specker, 2017; Polachek et al., 2017; Ugarte-Gil et al., 2017; van Vollenhoven et al., 2017). Nevertheless, the best definition of such conditions is still under debate and not widely shared.

Recently, Jesus et al. (2019a) developed a new score to measure disease activity, named SLE Disease Activity Score (SLE-DAS) (Jesus et al., 2019a). This score encompasses 17 items and includes some continuous variables (Jesus et al., 2019a). When comparing the performance of this instrument with the SLE disease Activity Index 2000 (SLEDAI-2K) (Gladman et al., 2002), the Authors found that SLE-DAS has a higher accuracy in measuring SLE disease activity, a better sensitivity-to-change and a higher predictive value for damage accrual (Jesus et al., 2019b). Other advantages are that SLE-DAS is a continuous measure of disease activity and includes two important features absent in the SLEDAI-2K, i.e. haemolytic anaemia and lupus enteritis (Jesus et al., 2019a).

During pregnancy, some maternal physiological changes can occur and consequently mislead the evaluation of disease activity. Hence, scoring SLE activity by applying the SLEDAI-2K could be biased. For this reason, Buyon et al. proposed a modification of SLEDAI-2K, which is named SLEPDAI (Buyon et al., 1999). Nonetheless, this score has never been validated.

Since no data on SLE-DAS applicability during pregnancy are available, we aimed to evaluate SLE-DAS in the first trimester as predictor of maternal flares and obstetrical complications.

MATERIALS AND METHODS

Patients

This study was carried out at two referral centers for rare systemic and autoimmune diseases: Rheumatology Unit, University of Padova, Italy (from 2002 to July 2019), and Internal Medicine Department, Cochin Hospital, Paris, France (from 2014 to July 2019, by using all pregnancies from the prospective GR2 study clinicaltrial.gov NCT02450396).

Inclusion criteria were 1) women ≥18 years; 2) affected with SLE (SLICC 2012 criteria) (Petri et al., 2012); 3) with an ongoing singleton pregnancy at 12 weeks (only one pregnancy per patient).

Patients underwent at least one visit in the first trimester, and were followed up according to current clinical practice until the end of pregnancy. This project adheres to the principles of the Declaration of Helsinki and was approved by the local ethics committees.

Methods

Demographic, clinical and laboratory findings were collected at first trimester by assessing the following variables: age, disease duration (years), skin colour, multiparity, associated anti-phospholipid syndrome (APS) (Miyakis et al., 2006) and SLE manifestations.

Serological and other laboratory data were assessed at first trimester according to standard tests including anti-double stranded DNA (anti-dsDNA), C3 and/or C4 serum levels, and 24-hour (h) proteinuria. Anti-phospholipid (aPL) Abs were also tested including anti-cardiolipin (aCL) IgM and IgG, anti-ß2 glycoprotein-1 (anti-ß2GP1) IgM and IgG, and lupus anticoagulant (LAC) according to standard definitions (Miyakis et al., 2006) and recommendations (Moore, 2014).

Women were considered on therapy when they were taking at least one of the following drugs: hydroxychloroquine (HCQ), prednisone, immunosuppressants (IS), low dose aspirin (LDA) and low molecular weight heparin (LMWH).

Definition of Disease Activity

Disease activity was assessed at first trimester by applying SLEPDAI (Buyon et al., 1999) and by retrospectively applying SLE-DAS using the online free calculator available at http://sle-das.eu/ (Jesus et al., 2019a).

Definition of Maternal Flares

Maternal flares in the 2nd and 3rd trimester of gestation were assessed according to SELENA-SLEDAI flare index (SFI) (Petri et al., 2005); flares were subdivided into mild/moderate and severe.

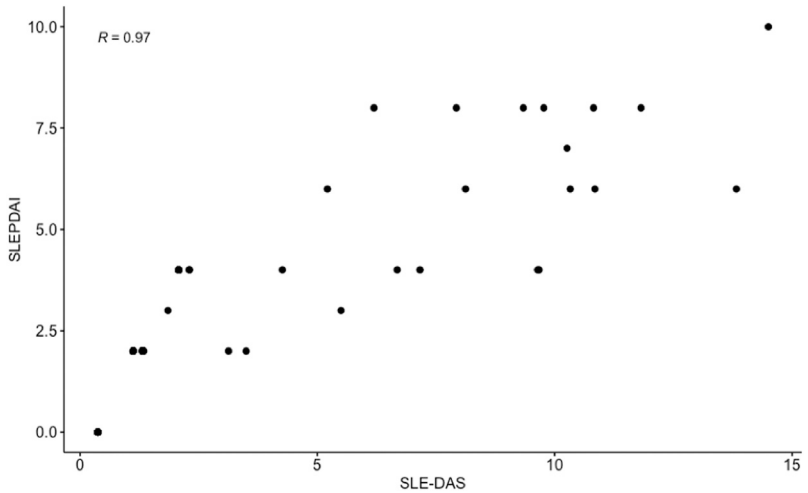


FIGURE 1 | Correlation between SLEPDAI and SLE-DAS at first trimester.

Definition of Adverse Pregnancy Outcome (APO)

APO were defined with a binary composite score obtained when any of the following event occurred: an otherwise unexplained intrauterine foetal death (IUFD) >12 weeks; a neonatal death within the first 7 days after birth; placental insufficiency (IUGR, PE/eclampsia -E-, Hemolysis, Elevated Liver enzymes, Low Platelets count -HELLP-syndrome, and/or placental abruption) leading to a premature delivery before 37 weeks; small for gestational age (SGA): birth weight ≤3rd percentile according the AUDIPOG curve (Mamelle et al., 2001). Definitions of PE and HELLP are summarized in **Supplementary Material**.

Statistical Analysis

We described patients' characteristics applying mean ± standard deviation (SD) and median with interquartile range (IQR) for parametric and non-parametric continuous variables, respectively. APO's and maternal flares' incidences was reported by confidence intervals (CI) set at 95%. The following variables were assessed at first trimester by univariate analysis:

- Continuous: age at pregnancy (years), disease duration (years), SLEPDAI and SLE-DAS scores, prednisone dosage (mg/day);
- Categorical/binary: associated APS, previous renal involvement, serological features including anti-dsDNA, hypocomplementemia (low C3 and/or C4), aPL profile (LAC, IgG/IgM anti-aCL, IgG/IgM anti-beta2GPI, triple positive aPL), active 24 h proteinuria (>0.5 g/day); concomitant treatment including HCQ, prednisone, IS, LDA, and/or LMWH.

Comparison of continuous variables with a parametric and non-parametric distribution was performed using T-test and Wilcoxon's rank-sum test, respectively. Pearson's chi-square (or Fisher's exact test when appropriate) was used to evaluate bivariate associations between categorical variables at univariate analyses. A correlation between SLEPDAI and SLE-DAS in the first trimester was assessed according to Spearman's correlation test, considering the non-parametric distribution of these scores. Multivariate analysis was performed according to a logistic regression model. The choice of independent variables was based on current knowledge and significant variables at univariate analysis ($p < 0.1$). Two separate multivariate analyses were performed for the outcomes of maternal flares and APO, respectively. Significance at logistic regression analysis was set at 5%. Models' performance was evaluated using the Hosmer–Lemeshow (HL) goodness-of-fit test and area under the ROC curve (AUC). All statistics were conducted using R software version package 1.3.1073.

RESULTS

General Features of SLE Pregnancies at First Trimester

A total of 158 pregnancies in 158 patients affected with SLE were collected (107 enrolled at Internal Medicine Department, Cochin Hospital, and 51 at the Rheumatology Department, University of Padova). Mean ± SD age was 31.9 ± 4.6 years, and 89 (56.3%) women were multiparous.

The majority were White (n = 124, 78.5%), followed by Black (n = 21, 13.3%), Asian (n = 11, 6.9%) and other origin (n = 2, 1.3%).

Previous SLE manifestations before pregnancy occurred as following: articular involvement in 125 (79.1%) women, mucocutaneous in 108 (68.4%), renal and haematological in 59 (37.3%) respectively, serositis in 36 (22.8%) and neuropsychiatric (NPSLE) in 7 (4.4%).

TABLE 1 | Maternal flares (2nd and 3rd trimester) and APO.

Patients with at least one flare, *n* (%)	25 (15.8)
Articular, *n* (%)	10 (6.3)
Mucocutaneous, *n* (%)	7 (4.4)
Renal, *n* (%)	5 (3.2)
Haematological, *n* (%)	3 (1.9)
Serositis, *n* (%)	3 (1.9)
NPSLE, *n* (%)	0 (0.0)
Patients with at least one APO, *n* (%)	19 (12.0)
IUFD, *n* (%)	4 (2.5)
Preterm delivery due to placental insufficiency, *n* (%)	13 (8.2)
SGA, *n* (%)	3 (2.0)
Neonatal deaths, *n* (%)	0 (0.0)

SLE: Systemic Lupus Erythematosus; NSPLE: Neuropsychiatric SLE; APO: adverse pregnacy outcome; IUFD: intra-uterine fetal death; SGA: small for gestational age.

Median SLEPDAI (IQR) was 2 (0–4) and median SLE-DAS (IQR) was 1.32 (0.37–2.08).

General Pregnancy Outcome

We observed 153 (96.8%) live births: their mean birth weight ±SD was 2,946 ± 583 g (2 missing data), and the median delivery term (IQR) was at 38 WG (36–39) (3 missing data). Four (2.5%) IUFD occurred and a medical termination of pregnancy was performed in 1 (0.6%) case.

Maternal Flares

At least one flare occurred in 25 (15.8%, 95% CI 9.9–20.9) patients during the 2nd and 3rd trimester: 23 (14.6%) women experienced mild/moderate flares and 2 (1.3%) severe renal flares. Overall, we observed that 10 (6.3%) patients had at least one articular flare, 7 (4.4%) mucocutaneous, 5 (3.2%) renal, 3 (1.8%) hematological and serositis flares, respectively. No NPSLE flares occurred in this study (**Table 1**).

APO

Nineteen (12.0%; 95% CI: 7.8–18.0) pregnancies were complicated by obstetrical events (**Table 2**). Four patients (2.5%) had an IUFD and 13 (8.2%) preterm deliveries due to placental insufficiency. In addition, 3 pregnancies (2.0%, 7 missing data) ended with SGA births. No neonatal deaths occurred.

Univariate Analyses

At univariate analysis, both SLE-DAS and SLEPDAI scores in the first trimester were associated with maternal flares in 2nd and 3rd trimester of gestation ($p = 0.01$ for both). In addition, anti-dsDNA ($p = 0.02$) and active 24 h-proteinuria ($p = 0.02$) were also found to be associated with maternal flares. Regarding treatment, the use of prednisone and prednisone dosage ($p = 0.04$ and $p = 0.02$, respectively) (**Table 2**). There was a high and significant correlation between SLEPDAI and SLE-DAS (rho = 0.97, $p < 0.01$) in the first trimester.

At univariate analysis, SLE-DAS ($p = 0.02$), SLEPDAI ($p = 0.02$) and anti-dsDNA ($p = 0.01$) were associated with APO (**Table 3**).

TABLE 2 | Univariate analysis: Maternal flares in the 2nd and 3rd trimester. Bold values refer to significative *p* values ($p < 0.05$).

	Overall (*N* = 158)	Flare (*N* = 25)	Non flare (*N* = 133)	*p* Value
Age at pregnancy, mean ± SD (years)	31.9 ± 4.6	31.4 ± 4.6	32.0 ± 4.6	0.50
SLE characteristics				
Associated APS, *n* (%)	18 (11.4)	1 (4.0)	17 (12.8)	0.31
Disease duration, median (IQR)	9 (5–13)	10 (2–13)	9 (5–13)	0.66
Previous renal manifestation, *n* (%)	59 (37.3)	9 (36.0)	50 (37.6)	0.88
Laboratory features in the 1st trimester				
Positive anti-dsDNA, *n* (%)	80 (50.6)	18 (72.0)	62 (46.6)	**0.02**
Low C3/C4, *n* (%)	54 (34.2)	9 (36.0)	45 (33.8)	0.83
24 h-proteinuria > 0.5 g/day, *n* (%)	12 (7.6)	5 (20.0)	7 (5.3)	**0.02**
IgG/IgM anti-cardiolipin, *n* (%)	22 (13.9)	3 (12.0)	19 (14.3)	1.00
IgG/IgM anti-beta2GPI, *n* (%)	12 (7.6)	1 (4.0)	11 (8.3)	0.69
LAC, *n* (%)	24 (15.2)	2 (8.0)	22 (16.5)	0.37
Triple positive aPL, *n* (%)	7 (4.4)	0 (0.0)	7 (5.3)	0.60
Treatment in the 1st trimester				
Prednisone, *n* (%)	72 (45.6)	16 (64.0)	56 (42.1)	**0.04**
Prednisone dose, median (IQR), mg/day	5 (5.0–7.5)	5 (0.0–7.0)	0 (0.0–5.0)	**0.02**
Immunosuppressants, n (%)	44 (27.8)	11 (44.0)	33 (24.8)	0.05
Hydroxychloroquine, *n* (%)	149 (94.3)	23 (92.0)	126 (94.7)	0.63
Low dose aspirin, *n* (%)	88 (55.7)	13 (52.0)	75 (56.4)	0.68
Low molecular weight heparin, *n* (%)	35 (22.6)	3 (12.0)	32 (24.1)	0.29
Disease activity in the 1st trimester				
SLEPDAI, median (IQR)	2 (0–4)	3 (2–6)	2 (0–4)	**0.01**
SLE-DAS, median (IQR)	1.32 (0.37–2.08)	1.85 (1.32–6.19)	1.32 (0.37–2.08)	**0.01**

SD: standard deviation; IQR: interquartile range; SLE: Systemic Lupus Erythematosus; APS: antiphospholipid syndrome; anti-dsDNA: anti-double stranded DNA; 24 h: 24 h; LAC: Lupus anticoagulant; aPL: anti-phospholipid antibodies; SLEPDAI: Systemic Lupus Erythematosus Pregnancy disease Activity Index; SLE-DAS: Systemic Lupus Erythematous disease activity score.

TABLE 3 | Univariate analysis: Adverse pregnancy outcome (APO). Bold values refer to significative *p* values ($p < 0.05$).

	Overall (*N* = 158)	APO (*N* = 19)	Non-APO (*N* = 139)	*P* Value
Age at pregnancy, mean ± SD (years)	31.9 ± 4.6	31.4 ± 5.2	32.0 ± 4.5	0.57
SLE characteristics				
Associated APS, *n* (%)	18 (11.4)	3 (15.8)	15 (10.8)	0.46
Disease duration, median (IQR)	9 (5–13)	12 (5.5–17)	9 (4.5–13)	0.12
Previous renal manifestation, *n* (%)	59 (37.3)	9 (47.4)	50 (36.0)	0.33
Laboratory features in the 1st trimester				
Positive anti-dsDNA, *n* (%)	80 (50.6)	15 (78.9)	65 (46.8)	**0.01**
Low C3/C4, *n* (%)	54 (34.2)	8 (42.1)	46 (33.1)	0.44
24 h-proteinuria > 0.5 g/day, *n* (%)	12 (7.6)	2 (10.5)	10 (7.2)	0.63
IgG/IgM anti-cardiolipin, *n* (%)	22 (13.9)	3 (15.8)	19 (13.7)	0.73
IgG/IgM anti-beta2GPI, *n* (%)	12 (7.6)	1 (5.3)	11 (7.9)	1.00
LAC, n (%)	24 (15.2)	5 (26.3)	19 (13.7)	0.17
Triple positive aPL, *n* (%)	7 (4.4)	1 (5.3)	6 (4.3)	1.00
Treatment in the 1st trimester				
Prednisone, n (%)	72 (45.6)	11 (57.9)	61 (43.9)	0.25
Prednisone dose, median (IQR), mg/day	5 (5.0–7.5)	5 (0.0–6.8)	0 (0.0–5.0)	0.16
Immunosuppressants, *n* (%)	44 (27.8)	8 (42.1)	36 (25.9)	0.14
Hydroxychloroquine, *n* (%)	149 (94.3)	19 (100.0)	130 (93.5)	0.60
Low dose aspirin, *n* (%)	88 (55.7)	13 (68.4)	75 (53.9)	0.23
Low molecular weight heparin, *n* (%)	35 (22.6)	6 (31.6)	29 (20.9)	0.38
Disease activity in the 1st trimester				
SLEPDAI, median (IQR)	2 (0–4)	2 (2–6)	2 (0–4)	**0.02**
SLE-DAS, median (IQR)	1.32 (0.37–2.08)	1.32 (1.32–2.08)	1.32 (0.37–2.08)	**0.02**

APO: adverse pregnancy outcome; SD: standard deviation; IQR: interquartile range; SLE: Systemic Lupus Erythematosus; APS: antiphospholipid syndrome; anti-dsDNA: anti-double stranded DNA; 24 h: 24 h; LAC: Lupus anticoagulant; aPL: anti-phospholipid antibodies; SLEPDAI: Systemic Lupus Erythematosus Pregnancy disease Activity Index; SLE-DAS: Systemic Lupus Erythematous disease activity score.

TABLE 4 | Multivariate logistic regression for maternal flares. Bold values refer to significative *p* values ($p < 0.05$).

		Model 1	Model 2
	Crude OR (95% CI)	AdjOR (95% CI)	AdjOR (95% CI)
SLE-DAS in the first trimester (increase per 1 unit)	1.2 (1.1–1.4)	**1.2 (1.0–1.3)**	—
SLEPDAI in the first trimester (increase per 1 unit)	1.4 (1.1–1.7)	—	**1.3 (1.1–1.6)**
Prednisone in the first trimester	2.4 (1.0–5.9)	0.9 (0.2–4.4)	0.8 (0.2–3.7)
Prednisone dose (increase per 1 mg/day)	1.1 (1.0–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)
Immunosuppressants in the first trimester	2.4 (1.0–5.8)	1.5 (0.6–4.2)	1.6 (0.6–4.2)
H-L goodness-of-fit[a]		0.90	0.88
AUC curve[b]		0.70	0.69

OR: Odds ratio; adjOR: adjusted OR; CI: Confidence intervals; SLE-DAS: Systemic Lupus Erythematosus disease Activity Score; SLEPDAI: Systemic Lupus Erythematosus Pregnancy disease Activity Index; PDN: prednisone; mg: milligrams; H-L: Hosmer-Lemeshow; AUC: Area under the Curve.

[a]*Refers to p value;*

[b]*Refers to AUC.*

Multivariate Analyses

Regarding maternal flares, since both anti-dsDNA and active 24 h-proteinuria are components of SLEPDAI and SLE-DAS, we did not include these two variables into our logistic regression models in order to avoid collinearity issues. As we found a high correlation between SLEPDAI and SLE-DAS in the first trimester, two different logistic regression models were performed using SLEPDAI and SLE-DAS as explanatory variables (**Table 4**).

SLE-DAS in the first trimester was predictor of maternal flares in the 2nd and 3rd trimester (adjusted-adj-OR:1.2; 95% CI:1.0–1.3; $p = 0.02$). Also, SLEPDAI resulted predictor of maternal flares in pregnancy (adjOR = 1.3; 95% CI:1.1–1.6; $p = 0.01$).

We did not perform a multivariate analysis for APO as only anti-dsDNA, SLEPDAI and SLE-DAS resulted statistically associated at univariate analysis; therefore, due to collinearity issues a multivariate analysis was not assessed.

DISCUSSION

In this study of 158 pregnant women affected with SLE we analyzed disease activity in the 1st trimester assessed by SLEPDAI and SLE-DAS. Although 59 (37.3%) patients had had a previous renal involvement, SLE activity during the 1st trimester was mild: median (IQR) SLEPDAI of 2 (0–4) and median (IQR) SLE-DAS of 1.32 (0.37–2.08). Even though remission/LDAS state cut-off definitions in pregnant patients have not been validated yet, the low scores observed in disease

activity indexes in our study, suggest that most patients were not active in the first trimester.

Twenty-five (15.8%) women experienced at least one flare in the 2nd and 3rd trimester. Among them, the majority of our patients had mild/moderate flares (n = 23, 14.6%), and only 2 women (1.3%) developed severe flares. This is in line with the PROMISSE study which reported mild/moderate flares occurred in 22.3% and severe flares in 5.5% of SLE patients during 385 prospective pregnancies (Buyon et al., 2015).

APO occurred in 12% of patients, which is also in keeping with the PROMISSE study where these complications occurred in 19% of cases (Buyon et al., 2015). Finally, a high rate of live births was found (96.8%), probably due to the high rate of LDAS/remission state observed in the first trimester of pregnancy in our study. Hence, our results strengthen that remission or LDAS in the early pregnancy is important to avoid fetal complications during pregnancies (Andreoli et al., 2017).

A high correlation between SLE-DAS and SLEPDAI in the 1st trimester was observed in our cohort ($\rho = 0.97$, $p < 0.01$). This is in line with previous findings (Jesus et al., 2019a) who reported a high correlation between the SLE-DAS and SLEDAI-2K. SLEPDAI (Buyon et al., 1999) is a non-validated score adapted to pregnancy that includes the 24 items from the SELENA-SLEDAI with modifications of 15 of them, to avoid wrongly attribution of some physiological or pathological pregnancy changes to SLE (Buyon et al., 1999; Andreoli et al., 2019). Even if SLEDAI-2K and SELENA-SLEDAI are slightly different, correlation between SLE-DAS and both scores was therefore expected.

In multivariate analyses, both SLE-DAS and SLEPDAI at first trimester of pregnancy were independent predictors of SLE flares in the 2nd and 3rd trimester (adjOR, 95% CI = 1.2 (1.0–1.3); adjOR 95% CI = 1.3 (1.1–1.6). In addition, performance of both scores was assessed by AUC and Goodness-of-fit analysis which proved that SLE-DAS model performs slightly better than SLEPDAI model (**Table 4**). Thus, the high correlation between SLE-DAS and SLEPDAI, the predictive value of SLE-DAS for lupus flares, as well as the aforementioned performance models' tests prove that SLE-DAS is an appropriate instrument for monitoring SLE disease activity during pregnancy.

Both SLE-DAS and SLEPDAI were associated with APO at univariate analysis (p = 0.02), but since anti-dsDNA is already included in both scores, no multivariate analysis could be done. Although our patients had mainly inactive mild SLE, our results suggest that active SLE may still be associated with poor obstetrical prognosis. Such association between disease activity and APO has been already observed in elderly cohorts in which patients had a more active SLE (Clowse et al., 2005). These findings has led to current EULAR recommendations which pinpoint the importance of a stable mild/inactive disease when pregnancy is planned (Andreoli et al., 2017).

Our study has some limitations. First, we applied SLE-DAS retrospectively. This was unavoidable since SLE-DAS was validated in 2019 (Jesus et al., 2019a). Second, in keeping with current recommendations (Andreoli et al., 2017), most pregnancies occurred in patients in clinical remission or LDAS, therefore limiting the possibility to demonstrate a stronger association between high disease activity and APO. The strengths of this study also need to be remarked: first, this a quite large multicentric cohort from 2 referral centers in SLE; second, we acknowledged the role of SLE-DAS as a very simple tool to define disease activity in pregnant patients.

In conclusion, SLE-DAS in the first trimester may be a useful instrument to predict maternal flares in the 2nd and 3rd trimester.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Azienda Ospedaliera-Università degli Studi di Padova and CPP Ile de France VI. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML contributed to the conception and design of the work, the follow-up of patients, acquisition, analysis and interpretation of data and she drafted the work; NC-C contributed to the conception and design of the work, the follow-up of patients, and the revision of the manuscript for important intellectual content; GG-I, VG, NM, and LI followed up patients; DJ and LI helped in revising the work; AD contributed to the conception and design of the work, interpreted the data and revised the manuscript for important intellectual content. All the authors approved the final version of the manuscript and gave their agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.660123/full#supplementary-material.

REFERENCES

Andreoli, L., Bertsias, G. K., Agmon-Levin, N., Brown, S., Cervera, R., Costedoat-Chalumeau, N., et al. (2017). EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann. Rheum. Dis.* 76, 476–485. doi:10.1136/annrheumdis-2016-209770

Andreoli, L., Gerardi, M. C., Fernandes, M., Bortoluzzi, A., Bellando-Randone, S., Brucato, A., et al. (2019). Disease activity assessment of rheumatic diseases during pregnancy: a comprehensive review of indices used in clinical studies. *Autoimmun. Rev.* 18, 164–176. doi:10.1016/j.autrev.2018.08.008

Buyon, J. P., Kim, M. Y., Guerra, M. M., Laskin, C. A., Petri, M., Lockshin, M. D., et al. (2015). Predictors of pregnancy outcomes in patients with lupus: a cohort study. *Ann. Intern. Med.* 163, 153–163. doi:10.7326/m14-2235

Buyon, J. P., Kalunian, K. C., Ramsey-Goldman, R., Petri, M. A., Lockshin, M. D., Ruiz-Irastorza, G., et al. (1999). Assessing disease activity in SLE patients during pregnancy. *Lupus* 8, 677–684. doi:10.1191/096120399680411272

Clowse, M. E. B., Magder, L. S., Witter, F., and Petri, M. (2005). The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum.* 52, 514–521. doi:10.1002/art.20864

Fischer-Betz, R., and Specker, C. (2017). Pregnancy in systemic lupus erythematosus and antiphospholipid syndrome. *Best Pract. Res. Clin. Rheumatol.* 31, 397–414. doi:10.1016/j.berh.2017.09.011

Franklyn, K., Lau, C. S., Navarra, S. V., Louthrenoo, W., Lateef, A., Hamijoyo, L., et al. (2016). Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann. Rheum. Dis.* 75, 1615–1621. doi:10.1136/annrheumdis-2015-207726

Gatto, M., Zen, M., Iaccarino, L., and Doria, A. (2019). New therapeutic strategies in systemic lupus erythematosus management. *Nat. Rev. Rheumatol.* 15, 30–48. doi:10.1038/s41584-018-0133-2

Gladman, D. D., Ibañez, D., and Urowitz, M. B. (2002). Systemic lupus erythematosus disease activity index 2000. *J. Rheumatol.* 29, 288–291.

Jesus, D., Matos, A., Henriques, C., Zen, M., Larosa, M., Iaccarino, L., et al. (2019a). Derivation and validation of the SLE Disease Activity Score (SLE-DAS): a new SLE continuous measure with high sensitivity for changes in disease activity. *Ann. Rheum. Dis.* 78, 365–371. doi:10.1136/annrheumdis-2018-214502

Jesus, D., Rodrigues, M., Matos, A., Henriques, C., Pereira da Silva, J. A., and Inês, L. S. (2019b). Performance of SLEDAI-2K to detect a clinically meaningful change in SLE disease activity: a 36-month prospective cohort study of 334 patients. *Lupus* 28, 607–612. doi:10.1177/0961203319836717

Larosa, M., Del Ross, T., Calligaro, A., Favaro, M., Zanatta, E., Iaccarino, L., et al. (2019). Clinical outcomes and predictors of maternal and fetal complications in pregnancies of patients with systemic lupus erythematosus. *Expert Rev. Clin. Immunol.* 15, 617–627. doi:10.1080/1744666x.2019.1601557

Mamelle, N., Cochet, V., and Claris, O. (2001). Definition of fetal growth restriction according to constitutional growth potential. *Neonatology* 80, 277–285. doi:10.1159/000047157

Miyakis, S., Lockshin, M. D., Atsumi, T., Branch, D. W., Brey, R. L., Cervera, R., et al. (2006). International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J. Thromb. Haemost.* 4, 295–306. doi:10.1111/j.1538-7836.2006.01753.x

Moore, G. (2014). Recent guidelines and recommendations for laboratory detection of lupus anticoagulants. *Semin. Thromb. Hemost.* 40, 163–171. doi:10.1055/s-0033-1364185

Petri, M., Orbai, A. M., Alarcón, G. S., Gordon, C., Merrill, J. T., Fortin, P. R., et al. (2012). Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 64, 2677–2686. doi:10.1002/art.34473

Petri, M., Kim, M. Y., Kalunian, K. C., Grossman, J., Hahn, B. H., Sammaritano, L. R., et al. (2005). Combined oral contraceptives in women with systemic lupus erythematosus. *N. Engl. J. Med.* 353, 2550–2558. doi:10.1056/nejmoa051135

Polachek, A., Gladman, D. D., Su, J., and Urowitz, M. B. (2017). Defining low disease activity in systemic lupus erythematosus. *Arthritis Care Res.* 69, 997–1003. doi:10.1002/acr.23109

Pons-Estel, G. J., Ugarte-Gil, M. F., and Alarcón, G. S. (2017). Epidemiology of systemic lupus erythematosus. *Expert Rev. Clin. Immunol.* 13, 799–814. doi:10.1080/1744666x.2017.1327352

Ugarte-Gil, M. F., Wojdyla, D., Pons-Estel, G. J., Catoggio, L. J., Drenkard, C., Sarano, J., et al. (2017). Remission and Low Disease Activity Status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American Lupus Cohort (GLADEL). *Ann. Rheum. Dis.* 76, 2071–2074. doi:10.1136/annrheumdis-2017-211814

van Vollenhoven, R., Voskuyl, A., Bertsias, G., Aranow, C., Aringer, M., Arnaud, L., et al. (2017). A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann. Rheum. Dis.* 76, 554–561. doi:10.1136/annrheumdis-2016-209519

Zen, M., Iaccarino, L., Gatto, M., Bettio, S., Nalotto, L., Ghirardello, A., et al. (2015). Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann. Rheum. Dis.* 74, 2117–2122. doi:10.1136/annrheumdis-2015-207347

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership