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Pulmonary Consequences of Prenatal Inflammatory Exposures: Clinical Perspective and Review of Basic Immunological Mechanisms

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Chorioamnionitis, a potentially serious inflammatory complication of pregnancy, is associated with the development of an inflammatory milieu within the amniotic fluid surrounding the developing fetus. When chorioamnionitis occurs, the fetal lung finds itself in the unique position of being constantly exposed to the consequent inflammatory meditators and/or microbial products found in the amniotic fluid. This exposure results in significant changes to the fetal lung, such as increased leukocyte infiltration, altered cytokine, and surfactant production, and diminished alveolarization. These alterations can have potentially lasting impacts on lung development and function. However, studies to date have only begun to elucidate the association between such inflammatory exposures and lifelong consequences such as lung dysfunction. In this review, we discuss the pathogenesis of and fetal immune response to chorioamnionitis, detail the consequences of chorioamnionitis exposure on the developing fetal lung, highlighting the various animal models that have contributed to our current understanding and discuss the importance of fetal exposures in regard to the development of chronic respiratory disease. Finally, we focus on the clinical, basic, and therapeutic challenges in fetal inflammatory injury to the lung, and propose next steps and future directions to improve our therapeutic understanding of this important perinatal stress.

Keywords: chorioamnionitis, fetal lung, fetal inflammatory response, fetal immunity, immune ontogeny

INTRODUCTION

The epithelial surface of the lung is constantly exposed to external noxious stimuli, including pathogens, particulates, and toxins. To maintain function, the lung must be able to protect itself against or adequately respond to such insults. Failure of these defense mechanisms contributes to the development of disease, with potentially significant morbidity and/or mortality; in fact, respiratory diseases account for a substantial portion of the health burden faced by the global community (1–3). Though the incidence and prevalence of various diseases affecting the lung

change with age, lung illnesses occur in every stage of life. Exposure of the lung to infectious and inflammatory insults during both childhood and adulthood is well-known to cause chronic lung disease, but less well-recognized is the significant impact of exposure during the prenatal period *in utero*, when critical lung development processes are ongoing (4). Indeed, the developing mammalian lung is constantly exposed to amniotic fluid, and modifications in the amount or character of this fluid can lead to severe abnormalities in lung development (5, 6). The lung epithelium is so intimately exposed to amniotic fluid that early experiments have been successful in using intra-amniotic (IA) delivery to perform epithelial genome editing (7). A growing body of evidence suggests that many fetal exposures influence lung development, and that these exposures impact the trajectory of lung function changes in adolescence and adulthood, the risk of future respiratory disease, and how the lung responds to future injury.

This review seeks to summarize the evidence supporting the role of fetal lung inflammation on lifelong respiratory dysfunction through the prism of chorioamnionitis, a highly prevalent and extensively studied fetal injury. Herein we will review the clinical characteristics, mechanistic data, and experimental models underlying our current understanding of chorioamnionitis. We provide in depth review of the immunological consequences and discuss strengths and weaknesses of available animal models. Finally, we identify key future directions with the goal of furthering our understanding of fetal inflammation and *in utero* injuries to the lung. Our hope is that defining the key pathways and open questions will help optimize future translational science to provide better understanding of chorioamnionitis and other fetal inflammatory stressors, ultimately leading to improved therapies for affected patients.

FETAL ORIGINS OF LUNG DISEASE

It has been classically taught that lung function gradually declines throughout life for all individuals (8). However, this analysis assumed a common starting point for all adults and ignored exposures prior to the age of 25. In particular, as the perinatal period represents a still developing system undergoing proscribed, sequential changes leading to complete maturation, exposures occurring during this period afford more opportunity for injury-induced alterations than exposures that occur in the more static, homeostatic systems found in most organs later in life. This idea, termed the "fetal origins of disease" hypothesis, is supported by studies demonstrating that experiences early in life, including the antenatal period, impact a variety of adult health metrics (9–16) including lung function (17–21). Furthermore, the same injury occurring in this early life period may have a more dramatic impact than the same exposure occurring later in life, simply because they occur during an early developmental time point. This concept is supported broadly by the literature of developmental knockouts in mice, where germline or early knockouts of many genes leads to global, and often severe, phenotypes in affected animals. In humans, the fetal origins hypothesis may also explain the observation that individuals with similar genotypes can have widely variable manifestations of disease secondary to timing of injuries or environmental events. Such differential presentations may subsequently result in the clinical impression of sporadic disease, complex risk profiles for disease progression, or incomplete penetrance of clinical phenomena. One clear example of such time-related phenotypes has been described for the metabolic disease phenylketonuria (PKU). It is known that infants exposed to elevated phenylalanine levels *in utero* due to maternal PKU are at high risk for injury, especially severe neurologic impairment, regardless of their genetic profile (22–25). Similarly, those infants who are born with PKU have poor neurologic outcomes if their disease is not recognized and treated early (26). However, in those infants with PKU who are treated with dietary modification early in life, the consequences of non-adherence to therapy later in life present only with subtle cognitive impairments (27, 28). Thus, it appears the timing of exposure to high phenylalanine levels, rather than the presence of exposure, is of key importance in determining phenotype. It is likely that many diseases with presentation in the perinatal period are impacted by timing and dose effects in a similar manner.

In accordance with these data, and as predicted by the fetal origins of disease hypothesis, a number of retrospective cohort studies demonstrate lifelong risk for the development of cardiovascular, metabolic, respiratory, and other disease (29–36) following significant early life stressors, namely famine. Subsequent cohort studies focused specifically on lung disease suggest substantial connections between early life exposures and the development of adult lung illnesses, particularly chronic obstructive pulmonary disease and asthma (18, 37–40). Prenatal, perinatal, and childhood factors that are associated with worse respiratory outcomes during childhood include biomass fuel exposure (41, 42), tobacco exposure (42–45), air pollution (42, 46), preterm birth (46–50), and respiratory tract infections (46, 51), among others. Many of these same factors are similarly associated with adult lung function (52–54), suggesting that antenatal and perinatal factors during lung development can have lifelong impact. These exposures are thought to impact respiratory outcomes through direct effects as well as, and potentially more significantly, the provocation of an inflammatory response within the lung. We now turn to chorioamnionitis, a well-studied model of fetal inflammatory stress, to examine how *in utero* exposure to inflammation impacts the developing lung.

PATHOLOGICAL DEFINITION OF CHORIOAMNIONITIS

Chorioamnionitis is a technical, histopathologic term used to indicate inflammation of the placenta, specifically the chorion, amnion, or both (55). Up to 25–40% of preterm births are associated with chorioamnionitis (56, 57), and in very preterm infants (∼24 weeks gestation), the incidence of chorioamnionitis can reach over 90% (58, 59). In severe cases, the inflammation can include additional structures, namely the umbilical cord.

In the event of umbilical cord involvement, this inflammation is alternatively referred to as funisitis (59–61). Chorioamnionitis is classified according to both the qualitative degree of neutrophil infiltration within the placental membranes (grade 1–3) as well as the progression of neutrophil infiltration through the placental membranes (stage 1–3) utilizing the Redline criteria (61). Stage 1 and grade 1 chorioamnionitis are considered mild, whereas severe chorioamnionitis is defined by grade or stage >1 or the combination of chorioamnionitis and funisitis (61).

Importantly, histological chorioamnionitis is frequently clinically silent, with minimal maternal inflammatory response (62, 63). This is distinct from microbial invasion of the amniotic cavity, when culturable microorganisms are identified from amniotic fluid samples, and the placental and amniotic fluid inflammation is generally more severe (64). This is also different from the clinical diagnosis of chorioamnionitis, which is defined by manifestations such as intrapartum fever, maternal or fetal tachycardia, purulent or foul-smelling amniotic fluid or vaginal discharge, uterine tenderness, and maternal leukocytosis (65–68). In general, this review considers the literature with respect to the histological diagnosis, which is present in the majority of cases of *clinical* chorioamnionitis.

PATHOGENESIS OF CHORIOAMNIONITIS

The pathogenesis of chorioamnionitis has been a subject of investigation for decades. Initial hypotheses suggested microbial invasion of the amniotic cavity as the primary etiology (69). However, multiple subsequent studies have revealed that histological chorioamnionitis is often found in the absence of demonstrable infection (70, 71). Framed as "sterile intra-amniotic inflammation," chorioamnionitis is induced by some yet to be determined danger signal (72–74). Notably, bacterial colonization of the amniotic fluid without significant resulting inflammation has not been associated with negative effects (75). Conversely, inflammation without detection of bacteria has been associated with adverse clinical outcomes similar to those seen with the combination of inflammation and bacteria (75). These results strongly imply that chorioamnionitis is best understood as a severe inflammatory response in the amniotic space, rather than the reaction to a specific infectious agent, and that this inflammation, regardless of etiology, is the proximate cause of much of the morbidity and mortality seen in clinical chorioamnionitis.

MICROBIOLOGY OF CHORIOAMNIONITIS

Initial studies of the placental microbiome in subjects with severe chorioamnionitis showed particularly high abundance of urogenital and oral bacteria (notably *Ureaplasma parvum*, *Fusobacterium nucleatum* and *Streptococcus agalactiae)* and low levels of Lactobacilli (76). Further studies confirmed presence of urogenital and oral species, demonstrating strong correlation between severe chorioamnionitis and the presence of bacterial species, though specific species differ between studies (75, 77, 78). Using new techniques to study the microbiome, recent reports suggest microbial species diversity may be relevant, with diminished diversity in the placental membranes in severe chorioamnionitis compared to either mild chorioamnionitis or controls (76, 79). Severe chorioamnionitis was also associated with a significantly increased 16S rDNA copy number (79), suggesting a more robust infiltration of bacterial species overall. Nevertheless, these observations have been challenged by recent studies which found no distinction between negative background controls and placenta samples, even those from preterm births (80). A more recent study failed to detect any distinctive bacterial signature in placentas from cases of chorioamnionitis (81). While, *Ureaplasma* and *Mycoplasma* could be detected in the 16S rRNA gene sequence data from a small minority of preterm samples, these organisms were also usually detectable in vaginal swab samples from the same women, leaving it unclear whether these sequences originated from the placenta specimen or vaginal contamination during delivery.

CHORIOAMNIONITIS AND POSTNATAL HUMAN LUNG FUNCTION

An extensive literature documents the relationship of chorioamnionitis and lung function in the post-natal period. Initial studies identified a reduced risk of respiratory distress syndrome (RDS) but an increased risk of bronchopulmonary dysplasia (BPD) in preterm infants with chorioamnionitis (82). Tracheal lavage showed increases in inflammatory mediators including IL-1 in patients that developed BPD (83). Therefore, it was hypothesized that inflammation resulted in accelerated lung maturation, which explained decreased RDS, but had more long-term deleterious consequences on lung development, leading to increased risk of BPD. Since that time, multiple studies have tried to better delineate the relationship between chorioamnionitis, RDS, and BPD with mixed results. Multiple studies have confirmed the initial reports (68, 84–89), while recent meta-analyses have questioned the linearity of these relationships (90). A challenge in truly identifying the relationship between these pathologies is the lack of clarity in the ontogeny, diagnosis, classification, and treatment for each these disorders (91). Other confounding factors including gestational age and co-morbidities in the preterm population can also make these relationships difficult to quantify (91).

Supporting the impact of fetal inflammation on lung development, however, is the observation that exposure to the inflammatory state of severe chorioamnionitis is associated with adverse pulmonary outcomes in early childhood. In particular, a birth cohort followed through 2 years of age identified a strong joint effect of prematurity and chorioamnionitis on the risk of wheezing and asthma (92). This association may also partially drive the observed correlation between prematurity and wheezing and early life asthma seen in a subsequent meta-analysis of 31 different birth cohorts, though chorioamnionitis prevalence was not specifically reported (93). Additionally, a separate cohort demonstrates that exposure to severe

chorioamnionitis, but not mild chorioamnionitis, is independently associated with wheeze and respiratory-related physician visits in the first year of life (94), suggesting that the degree of inflammatory injury may be directed related to outcomes.

While there are no currently available studies that explicitly describe a connection between chorioamnionitis and late childhood, adolescent, or adult lung function, there are studies that demonstrate an association between coincident factors, namely BPD and prematurity, and later lung function. Prematurity has been variably associated with increased respiratory symptoms, airflow obstruction, and airway hyperresponsiveness into early adulthood (95–98). Similarly, BPD has been associated with airflow obstruction, increased medication use, and respiratory symptoms in childhood, adolescence, and early adults (99–103). Unfortunately, studies have not determined whether either of these two conditions contribute to accelerated lung function decline or more severe, deleterious responses to future noxious stimuli. However, it is likely that the observed reduction in peak lung function contributes to the emergence of chronic or classical adult symptoms earlier in life.

LUNG IMMUNE MILIEU IN HUMAN CHORIOAMNIONITIS

Despite the challenges in precisely correlating chorioamnionitis to specific lung diseases, it is clear that an *in utero* inflammatory environment impacts the development of the lung and predisposes later lung dysfunction. Our understanding of the mechanisms driving these epidemiological associations is limited, though several molecules have been implicated in lung injury in patients. Severe granulo-histiocytic infiltration (104, 105) and an increase in apoptotic cells (106) are found in chorioamnionitis- exposed infant's lungs at autopsy. During chorioamnionitis, the concentration of inflammatory mediators including IL-1β, IL-6, IL-8, MMP9 and TNFα in the amniotic fluid increases dramatically (82, 107–111). Immune cell numbers, especially neutrophils, are also more abundant in amniotic fluid (112–114). It is suggested that these amniotic fluid neutrophils are of fetal origin (115), though the subject remains controversial (112). Recently, immunophenotyping of cells isolated from chorioamnionitis-exposed amniotic fluid demonstrated an increased frequency of monocytes/macrophages, B cells, NK cells, and T cells in addition to confirming infiltration of neutrophils (64, 116), suggesting a multifaceted immune infiltrate. The associated inflammatory milieu negatively impacts surfactant composition and function (117), and alters response to therapeutic surfactant in patients with RDS (118). These multifaceted changes occur during the canalicular and saccular stages of lung development (∼16–36 wks), and it is tempting to hypothesize that injury at this time may impact alveolarization later in development, as supported by animal data (see below).

FETAL SYSTEMIC IMMUNE CONSEQUENCES OF CHORIOAMNIONITIS

In addition to the organ specific manifestations unique to the fetal lung, it is imperative to consider the systemic changes that can occur in response to chorioamnionitis. Of particular importance is the fetal immune system, as the fetal immune response can have a significant impact upon development and contribute to organ dysfunction. In fact, the most well-recognized effect of chorioamnionitis exposure on the neonatal immune system is the elevation of pro-inflammatory cytokines in fetal circulation. IL-6, generally considered the primary signal of fetal immune system activation, is frequently elevated in cord blood (119–121). This connection is notable enough that IL-6 was initially used to define an entity termed fetal inflammatory response syndrome (FIRS), the fetal corollary to adult systemic inflammatory response syndrome (SIRS). Other inflammatory mediators that are frequently elevated include TNFα, IL-1, and IL-8 (122–124). Importantly, while these mediators are significantly increased in infants exposed to severe chorioamnionitis, they are less elevated in mild chorioamnionitis (109, 125). This difference is likely in part due to the classification system of chorioamnionitis, as the histopathologic hallmark associated with FIRS is funisitis (121).

Beyond soluble mediators and histopathologic findings, transcriptional analyses have revealed several chorioamnionitis-induced alterations of the fetal immune system. Whole blood transcriptional analyses revealed ∼500 differentially expressed genes in chorioamnionitis compared to non-exposed neonates (126). Although the cellular source of differentially expressed genes was not determined, some of the top altered pathways pointed to activation of innate immune pathways in exposed neonates. In infants with chorioamnionitis, there was an increased proportion of total circulating monocytes (127), as well as neutrophils as far out as 6 days after birth (128). The increased levels of neutrophils could be due to the elevated plasma G-CSF in infants with FIRS (129). Cord blood neutrophils and monocytes in the context of clinical chorioamnionitis were found to have increased expression of TLR4 and TREM-1 (130). It was found that fetal bone marrow monocytes are distinct from adults (131). Besides numerous transcriptional differences observed, fetal monocytes were found to possess enhanced STAT phosphorylation in response in to IFNγ, IL-4, and IL-6 stimulation even at lower concentrations compared to adult monocytes (131). Although the consequences of these differences were not examined, it could suggest that fetal monocytes are highly sensitive to an inflammatory milieu it may encounter. However, analyses of *in vitro*-stimulated monocytes from chorioamnionitis-exposed neonates suggest blunted responsiveness. Indeed, RNAseq analyses of chorioamnionitis-exposed monocytes that were stimulated *in vitro* with *Staphylococcus epidermidis* uncovered a distinct transcriptional profile of hypo-responsiveness (127). In addition, chorioamnionitis exposure in preterm infants has also been shown to increase monocytic H3K4me3 methylation marks, which are tightly associated with inactive gene promoters (132). Monocytes from chorioamnionitis-exposed term infants with

increased H3K4me3 modifications produced less IL-1β, IL-6, and IL-8 when stimulated with LPS (132). These data are also in agreement with animal models of chorioamnionitis, which documented that intra-amniotic LPS induces maturation of fetal monocyte function, but long-term or repeated exposures to either LPS or *U. parvum* appear to drive *ex vivo* hypo-responsiveness (133, 134). Together, these data suggest that chorioamnionitis exposure contributes to monocyte dysfunction, with a dissociated phenotype, e.g., enhanced markers of activation directly *ex vivo*, but paradoxically, low response to further stimulation, which could drive the higher risk of sepsis related complications in these infants (127). Dendritic cells (DCs) are another population present in the fetus that are responsive to inflammatory signals such as TLR ligands (135). To our knowledge, their response to chorioamnionitis exposure has not been carefully analyzed, but it is likely that, as for macrophages, the inflammatory mediators present in the AF and the fetal circulation stimulate a fetal DC response that could potentially influence adaptive immunity. In addition, another cell population that intra-uterine inflammation induces is granulocytic myeloid-derived suppressor cells (GR-MDSC) (136), which may participate in chorioamnionitis-induced dysfunction of innate immune responses.

Analysis of adaptive immune responses in chorioamnionitis-exposed infants has mainly focused on T cells, in particular $CD4^+$ T cells. Chorioamnionitis exposure has been reported by several groups to drive the emergence of circulating T-effector memory cells ($CD4^+CD25^{lo}CD127^{hi}$), with a Th1/Th17-like phenotype (126, 137–139), although one study did not find such a difference (66). Chorioamnionitis also changed the metabolic profile of $CD4^+$ T cells, altering metabolites that are part of the tryptophan catabolism and glutathione detoxification pathway, which could be linked to the enhanced development of a Th1 response (137). Enhanced CD4 production of IL-6 has also been reported (137, 140). The mechanisms driving the presence of activated T cells in the context of chorioamnionitis remain unclear, though a recent report showed increased number of activated maternal alloantigen-responsive T cells in preterm infants (141). These activated T cell appeared independent of chorioamnionitis, but this study did not distinguish mild vs. severe chorioamnionitis, which may explain the overall lack of association.

$FoxP3^+$ regulatory T cells (Treg) are an abundant $CD4^+$ T cell subset *in utero* (142–144) and are important to inhibit fetal T cell responses against self- and non-self-antigens, including maternal alloantigens (143). Therefore, they have been one of the most studied T cell populations in neonates. However, no consensus has yet been reached on the effect of chorioamnionitis on the frequency of Tregs, as chorioamnionitis has been associated with either no change (140, 145) or decrease (139) in Treg frequency. These discrepancies could be due to the use of different criteria to define chorioamnionitis in different studies. Additionally, difference in the age of preterm infants and the markers used to identify Tregs in each study have complicated interpretation.

There may be additional qualitative differences in the Treg population as a result of exposure to inflammation. Indeed, chorioamnionitis in preterm infants was associated with increased number of Tregs expressing the Th17 main transcription factor RORγt (146) or capable of producing IL-17A (139). Similarly, RORγt/FOXP3 mRNA ratio is increased in the blood of premature infants exposed to severe chorioamnionitis, but not to mild chorioamnionitis (138). Treg suppressive capacity was also diminished in late preterm infants exposed to severe chorioamnionitis (145). However, whether this diminished overall suppressive function is mechanistically due to the increased proportion of inflammatory Tregs remains to be determined.

ANIMAL MODELS OF CHORIOAMNIONITIS

Studies focused on human neonates have not yet clearly identified actionable mechanisms related to the diagnosis or management of chorioamnionitis. This is due in part to the inherent logistical and ethical limitations of clinical studies as well as notable challenges related to access to fetal organs. In the next section, we will describe the data generated through the currently available animal models of chorioamnionitis (e.g., mouse, rat, rabbit, pig, sheep, and non-human primate) and how they provide a more specific understanding of the pathophysiology of fetal amniotic inflammation (**Table 1**). **Figures 1**, **2** summarize our current knowledge on the development of the lung and aspects of the immune system across species, respectively. These studies have shown a wide-ranging effect of chorioamnionitis on a number of organ systems, including the heart, lungs, intestine, brain, eyes, and kidney (119, 121, 148, 150–152). Here, we will focus on what these models have taught us about fetal lung and immune system development, maturation, and activation after fetal inflammation which is summarized in **Figure 3**.

Rodents

With their short gestation period (∼20 days) and multiple offspring per litter, allowing for large studies, and the possibility of easily introduced genetic modifications, rodent models provide significant benefits to mechanistic studies. However, multiple caveats have limited their usefulness in the study of chorioamnionitis. First, there is a level of uncertainty of whether an inflammatory challenge reaches each pup equally in the setting of large group gestation. Second, the developmental window of the rodent immune system is distinct from humans. Indeed, as shown in **Figure 2**, hematopoiesis and development of immune cells starts *in utero* at ∼5 weeks in humans, and ∼day 8 in mice (153, 154). Additionally, organization of secondary lymphoid organs such as the spleen (follicles and T cell zones) occurs *in utero* in humans while it only occurs late in gestation and post-birth in rodents (155–158). Thus, immunological studies in preterm rodents likely will not accurately reflect preterm human neonates.

The timeline of lung development is more similar between rodents and humans, but differences do exist. The majority of lung development occurs *in utero* for both species with the canalicular-saccular phase in mice (∼17days—birth) reflecting changes occurring during the 15–38 weeks of gestation in humans (159, 160). However, alveolarization begins during late gestation in humans (36 weeks) and only postnatally in the mouse (post-natal day 4) (4, 161). In addition, studies of fetal lung inflammation are hindered by the small size of rodent

TABLE 1 | Species comparison of animal models of chorioamnionitis to clinical observations in humans.

Model	Human	Rhesus macaque	Sheep	Pig	Rabbit	Rodent
Gestational period	280 day	~165 days	~150 days	~115 days	~32 day	~20–22 days
Placenta type	Discord, Hemochorial	Discord, Hemochorial	Cotyledonary, Epitheliochorial	Diffuse, Epitheliochorial	Discord, Hemochorial	Discord, Hemochorial
Agents used to induce chorio	Various microbes and/or mediators (absence of microbes, sterile inflammation) implicated	LPS, IL-1, Ureaplasma, TNFα	LPS, Ureaplasma, TNFα, L-1	*E. coli*, LPS	*E. coli*, LPS, IL-1	*E. coli*, LPS, IL-1
Pros of model		1. Similarity in organ, immmune ontogeny 2. Avalability of reagents	1. Similarity in organ, immune ontogeny	1. Multiple pups per litter	1. Short gestation 2. Multiple pups per litter	1. Short gestation 2. Multiple pups per litter 3. Availability of reagents 4. Different genetic models
Cons of model	Limited access to samples besides cord blood	1. Expensive (housing, maintenance, etc.) 2. Large studies to acquire sample sizes	1. Limited reagents 2. Expensive (housing, maintenance, etc.) 3. Large studies to acquire sample sizes	1. Challenge reaching the pups equally (multiple amniotic sacs) 2. Limited reagents	1. Challenge reaching the pups equally (multiple amniotic sacs) 2. Limited reagent 3. Unknown immunity pre-birth	1. Challenge reaching the pups equally (multiple amniotic sacs) 2. Small size pre-term (technical issues)

Refs: Furukawa et al. (147); Kallapur et al. (148); Kim et al. (59); Grigsby et al. (149).

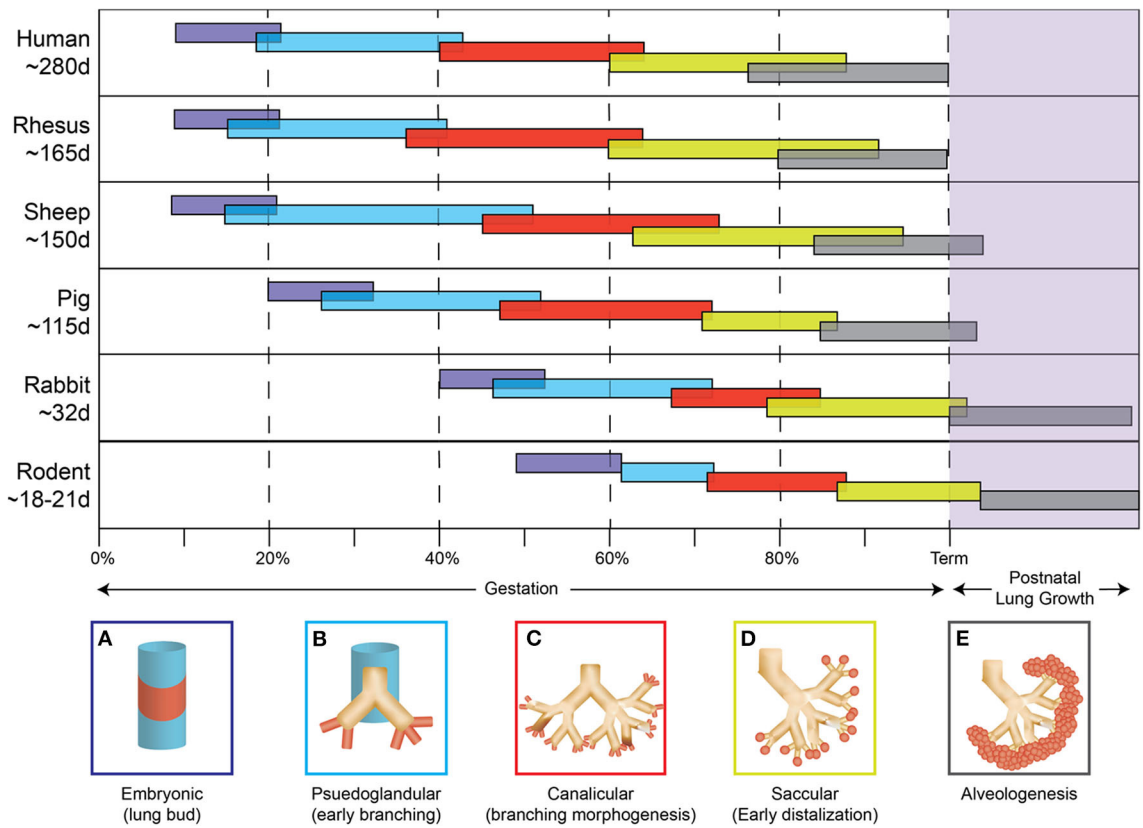

FIGURE 1 | Species comparison of lung development. The five stages of lung development **(A)** embryonic, **(B)** pseudoglandular, **(C)** canalicular, **(D)** saccular, **(E)** alveologenesis during gestation and postnatally are compared between different animal models used to study chorioamnionitis.

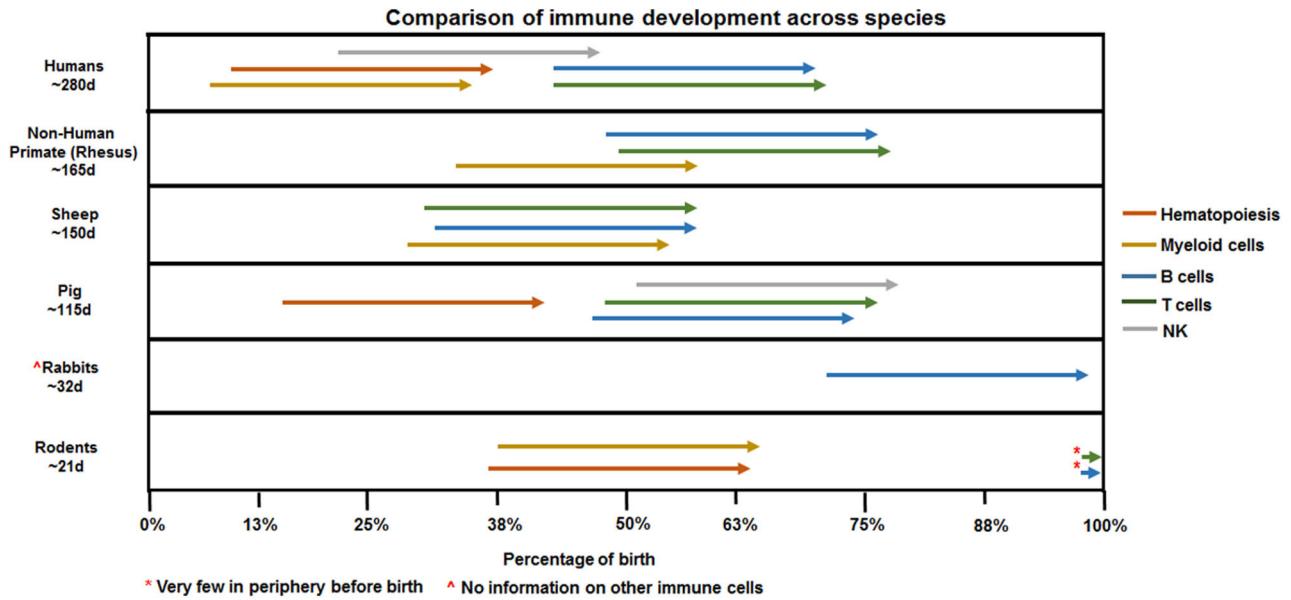

FIGURE 2 | Species comparison of immune ontogeny. Arrows denoting hematopoiesis or macrophages reference presence in AGM/yolk sac (human, rodent, pig) or fetal periphery (non-human primate, sheep). NK, T, and B cell arrows mark appearance in the fetal periphery outside of primary lymphoid organs such as bone marrow (NK, B cells) or thymus (T cells).

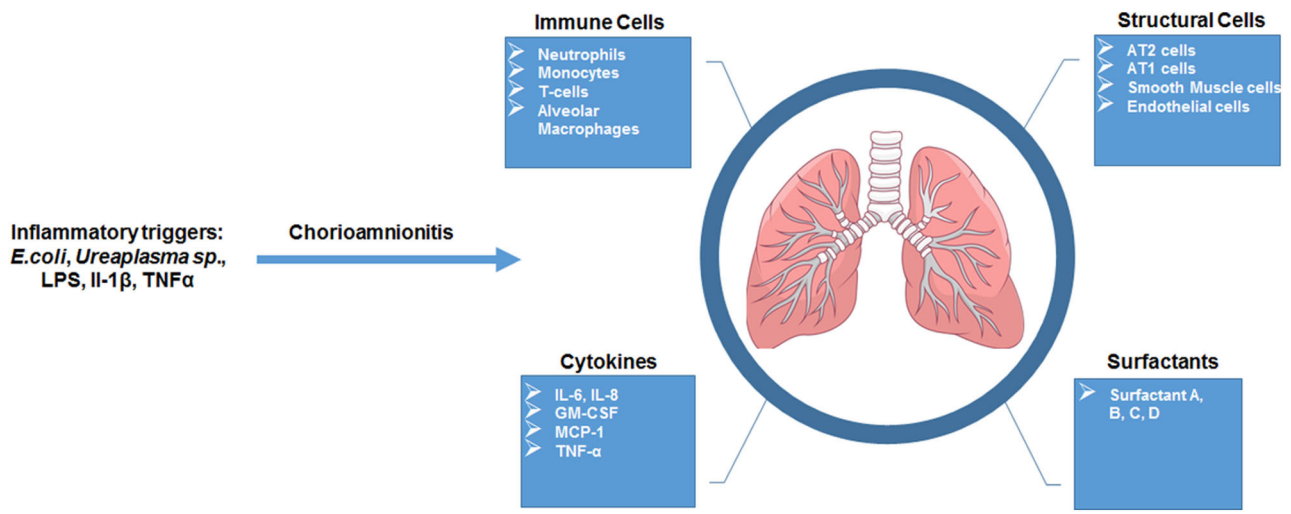

FIGURE 3 | Overview of fetal lung consequences in response to *in utero* inflammatory challenge. Summarized schematic of observations made of the fetal lung response in animal models of chorio.

pups, which can make extensive lung processing/manipulation technically challenging. Despite these differences, the rodent model has provided important clues on how inflammation impacts fetal and neonatal lung development.

IA injections of LPS and IL-1β in mice (162, 163) and rat (164) as well as endocervical injection of *E. coli* (165) have been used to induce chorioamnionitis in mice. Several characteristic features of human chorioamnionitis are recapitulated in these models, including neutrophilic infiltration in the placental membranes (163–165) and elevated IL-1β and TNFα in the amniotic fluid (162). There were also alterations to the fetal lung including neutrophil invasion, increased cytokine expression, decreased alveolarization (in those sacrificed post birth) with increased number of alveolar type II cells, the main source of surfactant proteins required for alveolar function (162, 165–168). These structural changes mirror those seen in the retrospective human studies reviewed above.

Given the role of IL-1β identified in early studies, novel mouse models have been generated to better understand this relationship mechanistically. Over-expression of human IL-1β in

fetal lung epithelium (169) was sufficient to increase neutrophil and macrophage infiltration to the lung and led to thickening of the saccular septa and airway wall, decreased elastin deposition, poor vascularization of developing alveoli, and hyperplasia of bronchial smooth muscle cells and goblet cells (170). These animals also showed decreased septation, resulting in fewer alveoli by post-natal day 7 (170), consistent with data from LPS and *E. coli* treatment models.

The effect of double hits, namely chorioamnionitis and hyperoxia, has also been explored in rodents. Interestingly, moderate hyperoxia improved lung function in rats exposed to intra-amniotic LPS, whereas severe hyperoxia further reduced it, highlighting the concept that the type of post-natal care, notably of post-natal ventilation, will also influence the overall outcome (163).

Rabbit

Similar to rodents, rabbits constitute a useful model for several reasons including size, multiple kits per litter, and short gestation (∼31 days). The 21–29 day age range of rabbits used in preterm studies (171–174) spans the canalicular and saccular phases of lung development, corresponding to ∼15–38 weeks in humans (175). Theses similarities in prenatal lung development make the rabbit an attractive model.

Little is known about the status of the rabbit's fetal immune system besides work detailing rabbit B cell biology (176–179). The peripheral blood of post-natal day 1 kits contained lymphocytes, neutrophils, monocytes, eosinophils, and basophils (180). In addition, lymphocytes from the peripheral blood, spleen, and mesenteric lymph node from these kits proliferated in response to ConA stimulation and produced antibodies following immunization (181), suggesting that the fetal immune system of rabbits is more developed at birth than that of rodents.

Intrauterine *E. coli* in rabbits induced neutrophil infiltration and even necrosis in the placenta (171, 174, 182, 183) along with elevated amniotic fluid cytokines (184). Surprisingly, little cell infiltration into the lung was present at 16–30 h post intrauterine *E. coli* (182); another report showed a transient increase of polymorphonuclear neutrophils into the bronchoalveolar lavage fluid (BALF) of infected kits 0–5 days after exposure and confirmed limited cellular infiltration in lung tissue (174). Together, both studies suggest that there is an early, but mild, immune response in the fetal lung, which is less intense than human and mouse data would have predicted. Despite this limited immune response, *E. coli* treatment did lead to altered lung development similar to other models, predominantly compromised alveolarization with decreased secondary septa (173, 174). IA LPS or IL-1α led to neutrophil infiltration in amniotic and bronchoalveolar fluid, increased surfactant expression and enhanced lung compliance (170, 172), suggesting that inflammatory exposure leads to lung maturation in this model despite the mild immune response.

Pig

The pig is a larger animal, with a longer gestation period (∼115 days) and multiple piglets per gestation. Importantly, it is one animal model where the development of the immune system occurs before birth. As early as 30–60 days gestation, innate and adaptive immune cells have been found in umbilical cord and lymphoid organs (185–190). Additionally, the preterm piglets at ∼97–106 gestational days (191, 192) closely reflects the saccular phase of humans (∼24–38 weeks) (160, 193). However, despite these strengths, very few studies of chorioamnionitis have been conducted in this model.

The IA administration of *E. coli* (194, 195) or LPS (185, 191, 192) leads to leukocyte infiltration and increased pro-inflammatory cytokine expression in the placenta, the amniotic fluid, and the fetal circulation. Following 3 days of LPS exposure, increased CXCL8 and IL-1 expression as well as MPO^+ cells were found in the fetal lung (191), suggesting longer term exposure to fetal inflammation may mirror the more acute events seen in other, smaller models.

Sheep

A strong homology in lung architecture, protein structure, growth factors, and immunity between sheep and humans makes the sheep a very relevant model to study lung development and function (196–199). Ovine lung structures are quite comparable to their human counterparts, particularly for epithelial cell distribution, mast cells, and smooth muscle populations (200–202). The sheep lung also contains phagocytic cells that are capable of responding to pathogens. Sheep tracheal explants have shown mucus coverage, mucociliary clearance, and cell structure that are all similar to humans (203–205).

In sheep, IA LPS or IL-1β lead to lung inflammation characterized by cellular infiltration and maturation, and increased cytokine (GM-CSF, IL-6) expression. Similar to rodent models, inflammation improved lung maturation, but reduced alveoli number (134, 206–208). In contrast to the fetal mouse lung that contains more mature monocytes (209), the fetal sheep lung contains very low numbers of alveolar macrophages in absence of inflammation (210). However, akin to human fetal lung, monocyte/macrophages are recruited to the lung after IA LPS (211). In addition, IA LPS triggers GM-CSF expression in the fetal lung, which induces PU.1, a transcription factor responsible for monocyte to macrophage maturation (211). Mechanistically, the robust responses induced by LPS are partially mediated by IL-1β, as co-administration of IL-1RA diminished LPS-induced neutrophil and monocyte infiltration into the BALF, IL-6 expression, and SP-C expression in the lung parenchyma (212).

In contrast to LPS, exposure to live *Ureaplasma* elicits only a mild response in the fetal lung (213). *Ureaplasma* causes infiltration of neutrophils into the lung, but limited monocyte recruitment, and no change in expression of inflammatory cytokines or surfactant proteins (213). Chronic *Ureaplasma* exposure (≥45 days) leads to a more robust cell infiltration into the BALF, with increased lung expression of IL-1β and IL-8 and lung maturation, but does not affect lung alveoli and vascular development (214–217).

Non-human Primates (NHP)

NHP have several key characteristics that make them a model of choice to study chorioamnionitis. The singleton long gestation along with hemochorial placentation and the endocrine

events surrounding parturition in rhesus are similar to human pregnancy (147, 149). Importantly, the cervical and vaginal microflora of the female rhesus are remarkably similar to human [see (218) and references therein]. The anatomic similarity of the rhesus monkey chest wall to the human one generates a functional residual capacity which comprises a similar percentage of total lung capacity (219, 220) comparable to humans. Due to the similarities in the lung function and immunity (221, 222), rhesus macaques have also been used as preclinical models of house dust mite-induced atopic childhood asthma (223–225). Furthermore, analysis of the airway transcriptome in this model demonstrated a large transcriptomic overlap between macaques and humans (226).

IA IL-1β exposure during rhesus gestation cause a robust, neutrophil-dominated cellular infiltration in the lung associated with increased cytokine expression and elevated lung maturation markers like surfactant A, B, C and D, similar to the sheep model (227). There was also a modest increase in the plasma level of glucocorticoids that are known to induce fetal lung maturation (227, 228). IA injection of *Ureaplasma parvum* and *Mycoplasma* lead to colonization of the fetal lung and BALF (229, 230). Initial studies reported acute inflammation following *Ureaplasma* challenge in rhesus lungs (230). However, similar to what has been described in sheep, subsequent studies suggest that IA *U. parvum* causes only a very mild lung phenotype (229). The reasons for these divergent outcomes in primate models remain unknown, as the same *U. parvum* serovar and the same dose was used in both studies. Key differences in study design include different animal colonies, which could have influenced the microbiome of animals prior to injury, as well as the use of catheterized animals only in the first study. Of note, IA *Ureaplasma parvum* followed by post-natal ventilation lead to significant lung inflammation in fetal baboons (231). When observed, inflammation in the rhesus fetal lung was associated with extensive fibrosis, elevated level of α-SMA and TGFβ1, as well as SMAD, IL-1β, and OSM (231).

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Histological and clinical chorioamnionitis frequently occur together, though either can be present without the other (68). Despite similar nomenclature, their associated outcomes do not necessarily correlate, and the interchangeable terminology leads to confusion, likely contributing to the mild effect size noted in studies linking chorioamnionitis with respiratory comorbidities. Activation of the fetal inflammatory response in histological chorioamnionitis can potentially influence the development and maturation of the fetal immune system. This *in utero* exposure may "prime" the developing immune system, even in the absence of infection. Such a "priming" results in a more activated and mature immunophenotype, potentially increasing the susceptibility of infants to later childhood diseases, altering their response to vaccination, or contributing to the development of immunopathological disorders. Indeed, funisitis, and activation of fetal inflammatory response were associated with > 2-fold increased risk of developing BPD. It may, therefore, be more instructive to separate clinical chorioamnionitis from histological funisitis. These entities have distinct clinical outcomes and likely activate different physiological pathways (109, 125). We argue that decoupling the "mild" chorioamnionitis from the "severe" chorioamnionitis, and consider separating the analysis of cases including funisitis, may accelerate our understanding of how the fetal inflammatory response directs the maturation of the fetal/neonatal immune response. The relative contribution of chorioamnionitis to RDS and BPD, independent of risk presented by premature birth, needs to be quantified, as the incidence of chorioamnionitis exposure increases with increasingly premature infants (56, 232).

Second, as mentioned earlier, the role of the microbiome remains controversial. Nevertheless, it is possible that the resident microbiome in mothers affects the fetal immune response and its consequences. As the microbiome is quite variable among humans, future studies will need to address whether this variability also modulates the contribution of inflammatory *in utero* exposures on lifelong lung development.

Third, whether unique anatomical position, which brings the fetal lung in direct contact with the inflammatory mediators in the amniotic fluid, results in organ-specific responses is unclear. Whether lung specific alterations in immune cells (135) reflect the systemic changes or are due to local alterations in cytokine milieu needs to be investigated. Furthermore, propagation of the inflammation from the lung to other organs has been suggested in animal models. Indeed, an elegant study where LPS was administered IA, restricted to the lung (tracheal infusion), gut (stomach infusion), or skin (snout occlusion) demonstrated that resultant gut inflammation was induced by either direct contact of the gut or the lung surface (233), evidenced by mild injury in epithelial cell integrity, impaired epithelial differentiation, and loss of ZO-1 along with mild cellular infiltration. This is just an example of a larger question when it comes to FIRS and multi-organ involvement (119, 151); are there potential interactions between organ systems, and under what conditions? These questions therefore represent a priority, and they need to be addressed in relevant animal models.

Finally, the exact mechanism(s) which drive these adverse respiratory outcomes are not yet known, but recent evidence has implied epigenetic alterations in the setting of tobacco exposure, famine, and infections (234–241). Such epigenetic alterations, possibly due to inflammatory milieu or direct toxic effects in the lung, are prime candidates to explain durable, lifelong, and often subtle alterations in disease susceptibility. Despite this provocative connection, direct evidence supporting this hypothesis remains limited. Another potential mechanism is the fact that Th2 immunity appears critical for lung homeostasis in early post-natal period. IL-33 production gradually increases (starting from embryonic day 19 in mice) as a result of mechanical stresses induced by breathing, resulting in mechanical tension on alveolar type-2 cells (242, 243). IL-33 promoted Th2 immunity by directing the recruitment of ILC2 as well as OX40L expression on DCs (243). Since inflammatory cytokines, for example IL-1 and IL-6, limit Th2 responses (244, 245) it is conceivable that the chorioamnionitis-associated

pro-inflammatory phenotype may contribute to altered lung development by interrupting the normal lung-shaping Th2-responses, although this possibility remains to be formally tested. Finally, emerging evidence from murine developmental biology literature implies multiple critical waves of lung development, and inflammation at critical times likely impacts these developing lung structural cells alone. All of these possibilities need to be directly evaluated in future studies to precisely target future therapies.

In conclusion, the continued use of animal models is needed to advance our understanding of the various fetal complications due to chorioamnionitis exposure. Depending on the scientific questions asked and context specificities, different animal models will be more or less useful, and future studies need to start integrating the findings. For example, leveraging the similarities between humans and NHP in regard to the close intersection of the lung and the immune system, in combination with the ability to make genetic modifications in rodents, will provide a framework to better understand the impact of severe chorioamnionitis on the developing fetal lung. Then, major findings from animal models will have to be investigated in human neonates. These studies will require extensive longitudinal studies, in which the severity of chorioamnionitis exposure and its intersection with prematurity are well-documented. Clinical pulmonary outcomes need to be carefully monitored in these infants, through repeated questionnaires, high-end imaging and functional assessments. As lung development continues well into the second decade of life, such studies would necessarily require extensive long term follow up to fully characterize the influence of inflammatory *in utero* exposures on lifelong lung development. Only such integrated studies, spanning from animal models to the clinic, can bring enough understanding on how the fetal inflammatory response affects newborn lung maturation, to design new therapeutic strategies aimed at limiting the risk of progressing respiratory diseases in chorioamnionitis-exposed infants.

AUTHOR CONTRIBUTIONS

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