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Role of short interpregnancy interval, birth mode, birth practices, and the postpartum vaginal microbiome in preterm birth

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There have been widely documented beneficial role of vaginal Lactobacillus species as an important biomarker for vaginal health and healthy pregnancy progression. When translating this to clinical settings, pregnant women with low proportions of Lactobacillus and commensurately high proportion of rich and highly diverse abnormal microbiota are most likely to encounter negative pregnancy outcome such as preterm birth and postpartum complications. However, multiple literatures have also addressed this notion that the absence of a Lactobacillus-dominated microbiota does not appear to directly imply to a diseased condition and may not be a major determinant of negative obstetric outcome. Caesarian delivery is notably a risk factor for preterm birth and postpartum endometritis, yet recent data shows a trend in the overuse of CS across several populations. Growing evidence suggest the potential role of vaginal/uterine cleaning practice during CS procedures in influencing postpartum infections, however there is a controversy that this practice is associated with increased rates of postpartum endometritis. The preponderance of bacterial vaginosis associated bacteria vagitype at postpartum which persist for a long period of time even after lochia regression in some women may suggest why short interpregnancy interval may pose a potential risk for preterm birth, especially multigravidas. While specifically linking a community of microbes in the female reproductive tract or an exact causative infectious agent to preterm birth and postpartum pathologies remains elusive, clinical attention should also be drawn to the potential contribution of other factors such as short interpregnancy interval, birth mode, birth practices and the postpartum vaginal microbiome in preterm birth which is explicitly described in this narrative review.

KEYWORDS

short interpregnancy interval, birth mode, vaginal microbiome, postpartum infections, preterm birth, vaginal cleaning, caesarian delivery, vaginal delivery

Abbreviations
CS, caesarian section; BVAB, bacterial vaginosis associated bacteria; PPE, postpartum endometritis; PTB, preterm birth.

Introduction

The objective of the Human Microbiome Project (HMP) is to provide a detailed characterization of the structure and composition of the microbiome across various body habitats (1). About a decade after the inception of HMP, there has been an increasing interest in understanding the composition and function of the vaginal microbiome (VMB) and its contribution to pregnancy outcome. As recommended by HMP, DNA sequencing-based interrogation of the microbiome has provided better insight into the myriads of microbes inhabiting the vaginal econiche (2, 3). This approach has also been deployed in several vaginal microbiome studies (4, 5). From an ecological standpoint, it is well documented that a robust, *Lactobacillus*-dominated vaginal profile are considered optimal for healthy pregnancy outcomes whereas an increased diversity and richness of vaginal microbial community with high proportions of non-*Lactobacillus* dominated microbiota including several bacteria vaginosis associated bacteria (BVAB) are considered unhealthy and a potential risk factor for preterm birth (6), postpartum endometritis (7) and preterm premature rupture of membranes (8, 9). Hitherto, there has been several conflicting reports regarding the role of the vaginal microbiota in determining obstetric outcome. While some studies suggest a role for the vaginal microbiota in adverse pregnancy outcome such as preterm birth (10–14) and postpartum complication (15). Other studies suggests that the presence or lack of *Lactobacillus* vagitype may not be requisite for adverse pregnancy outcomes (16, 17). The maternal vaginal microbiome also plays an essential role in the initial colonization of newborn babies' microbiota and therefore the development of a healthy microbiota (18). Aside this, growing evidence also suggest that birth mode [Cesarean section (C-section) or vaginal delivery] play a critical role in the initial colonization of the infant microbiome and may be associated with long-term health outcomes (19). Short interpregnancy intervals also appear to be associated with increased risks for adverse pregnancy outcomes for women of all ages (20). All these factors are holistically drivers of the preterm birth cascade and are describe in this review. Here we examine the role of short interpregnancy intervals, mode of delivery, birth practices and the postpartum microbiome in preterm birth to emphasize the need to track and pinpoint other potential drivers of preterm birth and to provide a basis to recommend targeted strategies for restoring the reproductive health fitness of women of reproductive age.

Methods

Literature search and review procedures

Literature search was conducted in PubMed, Web of Science, Embase and Cochrane Library using multiple keywords both alone as well as in combination so that all factors that have received recent scientific attention is included. Birth mode, postpartum, vaginal microbiome, postpartum infections, preterm birth, vaginal cleaning, caesarian delivery, vaginal delivery, uterine cleaning, postpartum endometritis were important key words used. Peer-reviewed, English-language original study articles published in key papers addressing whether a given factor plausibly contributes to PTB were included. When selecting articles addressing vaginal preparation pre-CS, articles on WHO recommendations, randomized control trials and other articles supported by Cochrane review were included. Articles addressing similar factors contributing to preterm birth were excluded by focusing on more recent articles, web-based material were also excluded except from scientifically trustworthy sources [e.g., World Health Organization (WHO)]. All results were uploaded to EndNote for the literature selection. The reference lists of eligible articles were also screened to detect relevant articles that were not identified by the initial search strategy. As illustrated, **Figure 1** depicts a causal chain diagram addressing some underlying causes of preterm birth.

Vaginal microbiome and preterm birth

Preterm birth (PTB), defined by the World Health Organization (WHO) as the delivery of an infant before completed 37 weeks of gestation. PTB represents one of the major challenges facing obstetrics and a leading cause of neonatal mortality worldwide (21). Annually an estimated 15 million babies are born too early and approximately 1 million children die each year due to complications of preterm birth (22). Many of the causes of PTB are incompletely understood since more than 65%–75% spontaneous PTBs occurs with idiopathic onset (23, 24), thus clinical symptoms alone are not enough to predict or identify women at higher risk of PTB. PTB is common in certain maternal or fetal conditions, such as preeclampsia, intrauterine infection, cervical insufficiency, preterm premature rupture of membranes (PPROM), polyhydramnios, and fetal malformations (25). Previous miscarriage, multifetal gestation, young or advanced maternal age, assisted reproductive technology (ART), black race, smoking, extremes of body-mass index (BMI), and low socioeconomic status are known risk factors for PTB (23, 24). Disruption of the vaginal microbiota (vaginal dysbiosis) which are often asymptomatic in most women is notably a risk factor for PTB (26–28). As an illustration, prior research has demonstrated that bacteria activate the innate immune system of the reproductive tract and fetal membrane driving an inflammatory cascade that results in cervical remodeling and disruption of fetal membrane architecture resulting in PTB (29–32). Additionally, *in utero* microbial colonization of fetus

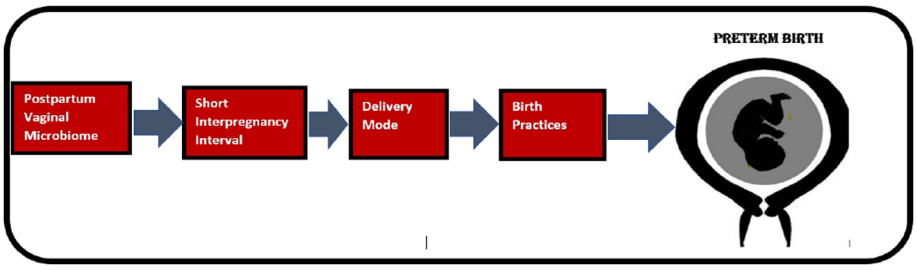

FIGURE 1
Causal chain diagram depicting some underlying factors that contribute to preterm birth.

has been suggested to play a substantial role in the early establishment of the infant's microbiome (18, 33). Conversely there have been other conflicting reports regarding the association of bacteria diversity with preterm birth outcomes. A longitudinal analysis of the vaginal microbiome in patients that encountered preterm birth revealed no difference in bacterial taxa associated with spontaneous preterm birth and term delivery (16). This report was further reinforced by the study of Elovitz and others (17) which addressed the notion that a non-*Lactobacillus* dominated flora may not be requisite for adverse pregnancy outcomes as some women with high level of vaginal bacterial diversity in this cohort delivered at term (17). *L. crispatus* is considered an optimal vaginal microbiome that supports healthy pregnancy progression (34), yet a Japanese cohort found L. *crispatus* as predominant microbes associated with women who delivered preterm (35). This inconsistencies and conflicting reports across studies are largely ethnically dependent and may have been reached due to variations in patients characteristics across various study cohorts; the definitions of PTB across low, low-middle- and high-income country; different cohort selection criteria (inclusion, exclusion, and elimination criteria) and diverse study designs, including different sequencing technologies and different 16S regions sequenced. Therefore, current research on microbiome and pregnancy should focus on better understanding of the dynamics within different cohorts/patients, as patient characteristics vary from study-to-study. Additionally, the role of the vaginal microbiome in the etiology of PTD remains to be delineated as such more attention should be drawn to the other potential factors that may contribute to preterm birth.

Role of birth mode in preterm birth

The maternal microbiome plays an essential role in the initial colonization of new-born babies and therefore the development of a healthy microbiota (18). Thus, the birthing process is a significant event in the initial seeding of the infant microbiome. Recent studies suggest that birth mode [Cesarean section (C-section) or vaginal delivery] is crucial in the initial colonization of the human microbiome and may be associated with long-term health outcomes (19). Immediately after birth, newborn babies experience rapid microbial colonization from their mothers and the surrounding environment (18), as such maternal Bacteroides strains, and opportunistic pathogens associated with the hospital environment are most likely transmitted to babies delivered by caesarean section (36, 37). To further corroborate this, a recent cross-sectional pilot study examined the association between a woman's birth mode and her vaginal microbiota in adulthood and found that women with low relative abundance of *Lactobacillus* spp. or women lacking a vaginal Lactobacillus profile had 3-fold increased odds of being born *via* C-section, indicating that C-section is associated with vaginal dysbiosis in adulthood (19). Further, an observational study across 10 different cohorts comprising of 1,033,3501 women demonstrated that pregnant women with history of previous cesarean section are significantly at a higher risk of preterm birth in subsequent births (38). To circumvent the incidence of preterm birth especially in women with history of Caesarian delivery the frequency of unnecessary cesarean section when there is no medical need should reduce. Health care system should also optimize the use of CS since underuse of CS may lead to maternal and perinatal mortality and morbidity and overuse of CS may create harm and potentially predispose to preterm birth.

Vaginal microbiome and postpartum infections

Infections at postpartum presents a significant burden to the hospital system and remains a significant cause of maternal mortality and morbidity worldwide (39, 40), yet the epidemiology of several post-delivery pathologies including postpartum endometritis, postpartum sepsis and chorioamnionitis remains elusive and has not been well

characterized. Postpartum endometritis (PPE) describes an inflammation or infection of the upper genital tract comprising the endometrium, myometrium, and the surrounding tissue. It typically involves multiple infectious agents ranging from a mixture of strict/facultative anaerobes to aerobes from the reproductive tract. Early postpartum endometritis occurs within (1–2 days) and infection that persists for more than 2 days are considered late postpartum endometritis (7, 41, 42). Several syndromes including fever, abdominal swelling, foul smelling lochia discharge, uterine tenderness, pain in the pelvis & lower abdomen, constipation, abnormal vaginal discharge, and vaginal bleeding are associated with postpartum endometritis (43–45). A global estimate of maternal death caused by several post-delivery infections reports a higher prevalence in countries with low-resources compared to high-resource settings (46, 47). Caesarian delivery is one of the major risk factors for PPE (40, 41). Prior research has shown that CS delivery introduces BVAB through surgical sites which follows a descending pathway into the vagina thus accentuating PPE (48) Consistent with this, Rosene and others (49) demonstrated that results from swabs and endometrial culture isolated from the genital tract of women with early postpartum endometritis predominantly comprises of microbes associated with vaginal dysbiosis including Mycoplasma, *Chlamydia trachomatis*, *Gardnerella vaginalis*, Peptococcus spp., Bacteroides spp., *Staphylococcus epidermidis*, group B Streptococcus, *Ureaplasma urealyticum* (49) *Clostridium sordellii* (50), *Clostridium perfringens*, streptococcal toxic shock syndrome (51) and *Leptrotrichia amnionii* a recently emerging pathogen of postpartum endometritis (52). DNA sequencing-based interrogation of the vaginal microbiome has vastly been studied in post-natal women (53–60). These studies have shown that a dramatic switch to a vaginal bacterial community lacking in *Lactobacillus* species is common after pregnancy (53–60). Although, majority of the aforementioned studies on the postpartum vaginal microbiome explored vaginal samples collected at 6 weeks postpartum (53, 54) and 1-week post-delivery (59), thus early postpartum microbiological content which could be potential biomarkers of early PPE are not accounted for. One potential way by which postpartum infections can be alienated is thorough screening of women for bacterial infection at late trimester. As an illustration, a recent study across a cohort of 61 Caucasian pregnant women at the first and third trimester of pregnancy investigated the distribution of *Gardnerella vaginalis* clades in the vaginal ecosystem and found a correlation between *Gardnerella vaginalis* clades and the whole vaginal microbiome (61). *Gardnerella vaginalis* is notable for been responsible for a significant number of infections in postpartum women worldwide and a leading cause of preterm birth and neonatal infection. Therefore, treating women with bacterial vaginosis at late trimester and screening asymptomatic women for bacterial vaginosis at late trimester should be considered to reduce the risk of PPE. To improve our understanding of the underlying epidemiology of PPE, future study should therefore consider early collection and investigation of swab samples few hours before and after surgical procedure (CS) or immediately after delivery especially for women with history of PPE.

Role of birth mode and birth practices in postpartum infections

There are multiple risk factors for postpartum endometritis including delivery mode (62), early and moderately preterm birth (63, 64), BMI (65), bacterial colonization with group A or group B *Streptococcus* (66), chorioamnionitis, prolonged rupture of membranes, prolonged operative time, poor nutrition, bacterial vaginosis, and multiple vaginal examination (67, 68). Of these risk factors associated with PPE, there are now substantial evidence linking the association of birth mode (CS or vaginal delivery) with PPE (40, 41). A Cochrane database review focused on understanding the etiology of endometritis after delivery demonstrated that postnatal women face a nearly 5–10 times greater risk of PPE following caesarean section compared to vaginal delivery (69). The prevalence of PPE is also higher in planned or emergency caesarean sections (1.5%–5%) compared to a lower prevalence (1.2%–2%) in vaginal deliveries (7, 70). Additionally, postpartum endometritis is primarily prevalent in 27% of cesarean deliveries and only 1%–3% of vaginal births (44, 62). PPE risks are also higher following caesarian deliveries performed in labor (3%–11%) compared to prelabor caesarian deliveries (0.5%–5%), as well as in patients with subsequent ruptured membranes compared to intact membranes (3%–15% vs. 1%–5%, respectively) (71). Caesarean section (CS) continues to evoke worldwide concern because of their steady increasing rates reaching up to 40.5% birth globally (72). According to new research from the World Health Organization (74, 75), caesarean sections now account for more than 1 in 5 (21%) of all childbirths. This number is set to continue increasing, with nearly a third (29%) of all births likely to take place by caesarean section by 2030 (73). While a caesarean section can be an essential and lifesaving surgery, it can put women and babies at unnecessary risk of short- and long-term health problems if performed when there is no medical need. With CS as a critical risk factor for PPE and with several literature reports of PPE potentiated by bacterial infections (76, 77), an important investigation of what practices are performed during CS surgical procedure could lends clue to the pathogenesis of PPE. PPE mediated by CS appears to be ethnically dependent. A recent analysis confirms the increasing trend of CS in all regions at different pace.

Subregions with the greatest increases were Latin America/Caribbean, Eastern Asia, Western Asia, Northern Africa (42.8-, 44.9-, 34.7- and 31.5%-point increase, respectively) while sub-Saharan Africa and Northern America (3.6- and 9.5%-point increase, respectively) had the lowest rise (74, 78, 79). This variation in the frequency of occurrence of postpartum endometritis mediated by CS across ethnically diverse groups in various populations may partly be due to variation in clinical settings, differences in individual or patients' characteristics especially in the context of susceptibility to infections and practices performed during CS procedures (79). While Lyon and Richardson (80) are of the school of thought that postpartum morbidities could be reduced by modifications in surgical technique (80). Epstein (81) is of the opinion that an alteration or modification in modern-day birthing surgical procedure has the potential of introducing new microbes that are non-susceptible to current antimicrobial therapy (81). In keeping up with this, there have been a lingering hypothesis that the practice of vaginal cleansing/vaginal preparation with vaginal antiseptic such as povidone-iodine and chlorohexidine before Cesarean delivery could reduce the rate of post-cesarean endometritis (82). Although the aforementioned trend analyses showed the underuse of CS in low-middle-income countries (especially sub-Saharan Africa), yet women in low, low-middle income countries appear to be more susceptible to postpartum infections caused by *E. coli*, *Proteus* spp., *N. gonorrhoea*, Group A and Group B *Streptococcus* and other strict Facultative anaerobes compared to women in high-income countries (HIC) (66, 83). The high incidence of postpartum endometritis in low-income settings compared to high income settings (83) may partly be due to the practice of not cleaning the vagina with cleaning antiseptics before cesarean delivery compared to high income settings where this practice is frequently performed. Support for the potential role of vaginal/uterine cleaning practice during CS procedures in influencing PPE comes from several reports showing that vaginal preparation or cleansing with povidone-iodine or chlorhexidine solution before cesarean delivery significantly reduced the incidence of post-cesarean endometritis (82, 84–86). A 2018 Cochrane Database systematic review published a study from a North American population demonstrated that that vaginal preparation or vaginal/uterine cleaning with povidone-iodine or chlorhexidine solution before cesarean delivery significantly reduced the incidence of post-cesarean endometritis (84). This observation is further corroborated in the study of (86, 87) which reported similar findings. Conversely, a randomized clinical trial across 648 patients (uterine cleaning group 336 patients and no cleaning group (312 patients) demonstrated that uterine cleaning after delivery of the placenta during CS can be omitted as a surgical step during the operation as cleaning was found associated with increased rates of postpartum endometritis and blood loss (88). In settings where vaginal/uterine cleaning is not practiced, there is a contention that since evidence-based guidelines recommended the administration of narrow-range prophylactic antibiotics (89) before or during the surgery/CS such antibiotic is of putative neonatal benefit and sufficient enough to decrease the risk of infection as such initial cleansing of the vagina before the procedure may not be necessary. Further there is also recent evidence supporting the use of pre-incision, broad-spectrum antibiotics, which result in a lower rate of maternal morbidity with no disadvantage to the neonate (90). Additionally, applying vaginal cleansing agents would mostly likely predispose patients to other side effects, allergies, and irritation symptoms (91), therefore cleaning may not be required. Further and future investigation/clinical trials across populations are required to better understand the potential role of vaginal/uterine cleaning practice during CS procedures in influencing PPE.

Postpartum vaginal microbiome, short interpregnancy interval, and its impact on multigravida

The microbiota of the female reproductive tract fluctuates throughout a women's lifespan and in response to circulating hormone levels. In women of reproductive age, rising estrogen levels promotes proliferation of vaginal epithelial cells and glycogen deposition which reduces the pH of the vaginal mucosa thus supporting the growth of Lactobacillus (92). Pregnancy is a unique phenomenon characterized by increasing placenta production of estrogen (93, 94) which potentiate lactobacillus drive with increasing gestational age (54). However, at the postpartum period there is a 100- to 1,000-fold dramatical decrease in steroid hormones (95) therefore any oestrogen-driven *Lactobacillus* sp. dominance of the vaginal microbiome during pregnancy is dynamically altered during the postpartum period to a vaginal microbiome depleted of *Lactobacillus* spp. and enriched with bacterial vaginosis associated species. This dynamism provides evidence that oestrogen is likely an important factor in shaping the composition of the vaginal microbiome, particularly during pregnancy (54, 96). Aside chemical modulation of the vaginal microbiome by steroid hormone. Duration, and cessation of lochia discharge is another important factor in shaping the vaginal microbial composition post-delivery (53). Lochia is an alkaline discharge that comprise of blood, serosa. This lochia-rich alkaline vaginal milieu during postpartum is a haven for the proliferation of *BVAB*. Discharge rates, volume, and cessation of lochia during post-delivery differs between subjects, but typically lasts about 6–8 weeks (97, 98) or more (99). This raises an important question of what period of time will any lochia driven BVAB vagitype revert to a Lactobacillus

state after lochia cessation. To provide a clue, the work of Doyle and colleagues (2012), have showed that quantities of Lactobacillus were yet depleted in the vaginal microflora of women followed up for a period of 1 year instead a preponderance of BVAB was found in the microflora of women previously dominated with *L. crispatus* during pregnancy (59). The preponderance of BVAB vagitype (a notable driver of PTB) for a long period of time after lochia regression, may suggest why short interpregnancy interval or conception within a short period may pose a potential risk for preterm birth to multigravidas irrespective of age (20). Therefore, spacing subsequent pregnancy beyond 18 months may be required to reduce the risk of preterm birth or negative pregnancy outcome in multigravida. To keep up with this, data from a cohort of 148,544 pregnancies reveal that interpregnancy intervals shorter than 18 months are associated with higher risks of adverse pregnancy outcomes for women of all ages (20). To further support this notion, a recent study from a Finnish population observed that preponderance of *L.* crispatus (compared to other species of Lactobacillus) was associated with only single birth per lifetime (primigravidas) compared to multigravidas with other lactobacillus spp or bacterial vaginosis associated vagitype that potentially increases the risk of premature delivery (100). The degree of protection conferred on the vaginal ecosystem is dependent on the predominant *Lactobacillus* species *L. crispatus* is considered optimal vaginal flora (101) as such the mechanism of transition to other vagitype during postpartum requires further investigation. Future study should investigate the period of restoration from the postpartum vaginal profile to the interpregnancy (normal) profile. A large longitudinal multicenter study is recommended to establish the composition of the postpartum vaginal microbiome accurately and to provide more insight into how a *Lactobacillus* profile is restored after lochia regression.

Discussion/future consideration

The inconsistency in reports regarding the role of the vaginal microbiome in preterm birth highlights the current poor understanding of how the vaginal microbiome may promote healthy pregnancy outcomes. A detailed assessment of the relative contribution of delivery mode, birth practice and the postpartum vagitype will be critical for designing of better targeted strategies to restoring the reproductive health fitness of women of reproductive age. Large cohort studies should be designed to focus on how a woman is birthed versus her maternal microbiome and the corresponding infant microbiome of her child to further elucidate the relationship between maternal microbiome, obstetric outcome, and fetal outcome. Based on evidence discussed here, we think that there is a correlation between how a woman is birthed and what become her vaginal microbiome composition at pubertal and postpubertal age which may potentially impact pregnancy outcome. In addition, we hypothesize that this effect may extend into future reproduction to impact pregnancy outcome. In clinical settings, the occurrence of unnecessary cesarean section should reduce to abate the incidence of preterm birth and unhealthy microbiota during adulthood in post pubertal women. More large multicenter clinical trials are required to affirm the relative contribution of delivery practices (vaginal cleaning) during CS to postpartum endometritis. Recently, chlorhexidine and povidone- iodine are recommended vaginal cleansing antiseptics as they have minimal side effects, with low rates of allergies or irritation symptoms (87). Given the risk associated with CS potentiated PPE, comparative studies and randomized clinical trials would be helpful in provide more knowledge on the role of vaginal cleansing in CS potentiated PPE. This can lend new clue and useful insight to understanding the underlying cause of the disparity in the prevalence of PPE in high- and low-income countries. As studies continue to shed light on the potential role of the vaginal microbiome, delivery mode and delivery practices in preterm birth, they should engage the research community, clinicians, and the public to reassess the impact of delivery mode and delivery practices in negative pregnancy outcome such as preterm birth and postpartum complications.

Author contributions

The author has made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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.

Publisher's note

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