Maternal health and the placental microbiome

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ABSTRACT

Over the past decade, the role of the microbiome in regulating metabolism, immune function and behavior in humans has become apparent. It has become clear that the placenta is not a sterile organ, but rather has its own endogenous microbiome. The composition of the placental microbiota is distinct from that of the vagina and has been reported to resemble the oral microbiome. Compared to the gut microbiome, the placental microbiome exhibits limited microbial diversity. This review will focus on the current understanding of the placental microbiota in normal healthy pregnancy and also in disease states including preterm birth, chorioamnionitis and maternal conditions such as obesity, gestational diabetes mellitus and preeclampsia. Factors known to alter the composition of the placental microbiota will be discussed in the final part of this review.

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1. The microbiome in pregnancy

Over the past decade, the role of the microbiome (i.e. the composite of microorganisms and its genomes on the body) in regulating metabolism, immune function and behavior in
humans has become apparent. The main focus of attention has been on the microbiota (i.e. the microorganisms present on a certain body site) of the gastrointestinal tract but microbiota are also present in the oral cavity, the skin, the lungs, the genitourinary tract and in pregnancy also in the placenta and the amniotic fluid.

The composition of the microbiome is dependent on body site, host-dependent factors including genetic make-up [1], dietary intake [2], disease state [3] as well geographic location [4] and bacterial species present [5]. For the gut microbiota, there is wide inter- and intra-individual diversity; however, a healthy gut microbiota in adults is mainly comprised of bacteria belonging to the phyla Firmicutes and Bacteroidetes. An imbalance in the composition of the microbiota is known as dysbiosis. Dysbiosis of the gut microbiota is associated with diverse disease states including inflammatory bowel disease, diabetes and asthma but also with obesity.

In pregnancy, the gut microbiota is altered with the progression of the pregnancy [6]. In the first trimester of pregnancy, the gut microbiota resembles that of outside pregnancy. At the start of the second trimester, abundance of specific bacterial genera have been associated with physiological parameters in the mother: abundance of Collinsella is positively correlated with blood pressure [8]. In the third trimester of pregnancy, the intra-individual diversity decreases with a higher abundance of bacteria belonging to the pro-inflammatory Proteobacteria phylum [6]. However, the inter-individual diversity increases in the third trimester due to the loss of different species in different women. When gut microbiota samples from women in the third trimester were transferred into a murine model, the mice became insulin resistant and gained weight, resembling the changes seen in pregnant women across gestation [6]. These results suggest that in pregnancy, the gut microbiota significantly contribute to the metabolic changes observed in the mother.

Until recently, the intra-uterine environment was considered sterile except in the case of pathological infections usually associated with adverse pregnancy outcomes including preterm birth. However, it is now clear that the placenta has its own microbiota and that this is not necessarily associated with infections. This review will focus on the current understanding of the placental microbiota in normal pregnancy and also in disease states including preterm birth, chorioamnionitis and maternal conditions such as obesity, gestational diabetes mellitus and preeclampsia. Factors known to alter the composition of the placental microbiota will be discussed in the final part of this review.

2. The placental microbiota in healthy pregnancy

2.1. The community composition of the placental microbiota in healthy term pregnancies

The role of the reproductive tract microbiome in pre- and post-conception is under current investigation [9]. Host-microbe and microbe-microbe interactions begin before birth. These interactions appear modifiable and are expressed as variability within, and between individuals.

The placenta is an organ that was previously considered to be sterile in the absence of clinical infection. However, more than three decades ago, the presence of bacteria within placental tissue was confirmed by cultivation-dependent techniques [10]. Since then, the presence of microorganisms within placental tissue has been described in the presence and absence of overt infection in cultivation-dependent and cultivation-independent (mainly PCR and 16S rRNA sequencing) studies (Table 1) [11–17]. Comparative studies report that cultivation-dependent studies likely significantly underestimate the incidence of microbial presence within the placenta, which is likely due to the presence of bacteria that are hard to culture due to their preference for anaerobic environments or requirement for specific unidentified nutrients [15,16,18–20].

More recent DNA-based studies provide evidence for the presence of a low biomass endogenous microbial community within the placenta [21]. The microbiota of placenta from healthy term deliveries have a high abundance of Lactobacillus sp., Propionibacterium spp. and members of the Enterobacteriaceae family [13,22,23]. Lactobacilli sp. are less abundant in placental tissues of preterm deliveries, possibly supporting a role for this genera in positive pregnancy outcomes [16].

2.2. Seeding of the placental microbiota: how do microorganisms and their products passage into the placenta?

It is still not entirely clear how microorganisms enter the placental fetal compartment. The current hypotheses is that microorganisms ascend from the vagina, maternal dendritic cells sample bacteria from the intestinal lumen which are internalized and transported to the placenta or enter via the blood supply to seed the microbiota of the placenta (Fig. 1) [24]. The evidence for vaginally-derived bacteria is strong and Lactobacillus–dominant microbiota, resembling the Lactobacilli sp. present in the vagina, are positively correlated with gestation age [21,25–27]. Bacterial translocation via dissemination through the blood supply is enhanced during pregnancy and lactation. Gaps in the epithelium in for example the intestinal and the oral mucosa enable the transfer of low numbers of bacteria into the circulation that can then seed the placenta [28]. The oral microbiota has recently been implicated as a primary source of placental bacteria; however, data comparisons were performed against oral microbiota data from an unrelated, non-pregnant population [21]. Animal studies have also demonstrated transmission of oral bacteria to the placenta [29,30], providing additional support for the seeding of the placenta microbiome from the oral cavity.

3. Other pregnancy microbiomes

Characterization of the vaginal microbiota using cultivation-independent techniques demonstrates significant individual variability [31]. Notably, the vaginal microbiota appears to become more stable as gestation progresses, with less intra-individual variability [13,32,33]. Further, the vaginal microbiota demonstrates enrichment of members of the orders Lactobacillales, Clostridiales, Bacteroidales and Actinomycetales [34]. This further supports a role for specific members of the microbial community in the prevention of preterm delivery [35,36].

The placenta is established within the uterus during early normal development. The non-pregnant, non-sterile uterus also harbors an abundance of DNA from the genera Lactobacillus, Bacteroides Gardnerella and Prevotella [37–40]. In comparison, cultivation-dependent studies identified Gardnerella, Lactobacillus spp. and Streptococcus spp. as the most abundant isolates in the absence of infection, and Lactobacilli, Gardnerella, anaerobic Gram-negative bacilli and anaerobic Gram-positive cocci in the presence of chronic inflammation [37,41]. An absence of correlation between the uterine microbiota and that of the vagina of the same woman has also been reported, highlighting niche-specific tropisms [37,39]. The microbiota of the pregnant uterus remains to be well characterized.
3.1. Roles for the placental microbiota

Interaction between the human host and her microbes is a significant contributor to the outcome of pregnancy [42]. The intra-amniotic immune response is a significant determinant of neonatal outcome associated with preterm delivery independent of gestational age [42–44]. There is evidence for the transfer of bacteria from the mother to the fetus, which is partially independent of the mode of delivery. The meconium of newborn infants delivered at term either vaginally or by Caesarean section contains commensal bacteria, including lactic acid producing species [45]. This suggests that the fetus is not sterile. Gram-positive cocci from a number of genera have been detected in cultures of umbilical cord blood collected from infants delivered by Caesarean section [46]. It is possible that the placental microbiota has a previously unconsidered role in early innate immune development. The

Table 1

<table>
<thead>
<tr>
<th>Site of detection</th>
<th>Amniotic fluid</th>
<th>Placenta membranes</th>
<th>Placenta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection method</td>
<td>Cultivation-dependent</td>
<td>Coagulase-negative staphylococci</td>
<td>Prevotella spp.</td>
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<tr>
<td></td>
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<td>Staphylococcus aureus</td>
<td>Staphylococcus spp.</td>
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<td></td>
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<td>Streptococcus agalactiae</td>
<td>Streptococcus pneumoniae</td>
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<td>Candida albicans</td>
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<td>Corynebacterium sp.</td>
<td>Escherichia coli</td>
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<td>Escherichia coli</td>
<td></td>
<td>Fusobacterium nucleatum</td>
<td>Gardinerella vaginalis</td>
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<td>Fusobacterium nucleatum</td>
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<td>Mycoplasma hominis</td>
<td>Mycoplasma hominis</td>
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<td>Gardnerella vaginalis</td>
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<td>Peptostreptococcus sp.</td>
<td>Peptostreptococcus sp.</td>
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<td>Mycoplasma hominis</td>
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<td>Streptococcus intermedius</td>
<td>Streptococcus sanguis</td>
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<td>Peptostreptococcus sp.</td>
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<td>Streptococcus viridans</td>
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<td>Streptococcus sanguis</td>
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<td>Ureaplasma urealyticum</td>
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<td>Streptococcus viridans</td>
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<td>Cultivation-independent</td>
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<td>Acinetobacter</td>
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<td>Parvimonas spp.</td>
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<td>Leptotrichia sp.</td>
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<td>Neisseria spp.</td>
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<td>Porphyromonas sp.</td>
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<td>Streptococcus intermedius</td>
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<td>Veillonella sp.</td>
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<td>Xanthomonas sp.</td>
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Fig. 1. Seeding of the placental microbiome.
maternal microbiota drives early innate immune development, and the placental microbiota is emerging as a source for antigenic determinants. Bacterial presence per se does not initiate adverse pregnancy outcomes, which further supports a positive role of placental microbe interaction with the mother and fetus [47]. In concordance with infectious disease studies, bacteria do not need to be viable to elicit an immune response. A recent murine study demonstrated the efficacy of host immune priming via microbial molecular transfer, in the absence of living bacteria [48]. This concept further supports the significance of identifying a low-biomass microbiota in the placenta. Animal studies support a role for neonatal immune priming and development in the absence of direct microbial exposure [48].

4. The placental microbiota and adverse pregnancy outcomes

4.1. The placental microbiota composition in pregnancies with adverse outcomes

Microbial invasion of the amniotic cavity is associated with significant neonatal and maternal morbidity and mortality [49]. Cultivation-dependent and independent studies have linked placental and amniotic fluid microorganisms with miscarriage, chorioamnionitis, preterm rupture of membranes, preterm delivery and stillbirth [21,50]. However, many of the ‘causal’ microorganisms and their DNA have also been detected in the placenta and amniotic fluid of women delivering at term and in the presence and absence of active labor [21,47,51]. Since gestational age is correlated with specific microbe species, it suggests that just as the placenta develops throughout gestation in response to environmental cues, so possibly does the placental microbiota [52]. It remains unclear whether alterations in the placental microbial communities observed in preterm delivery are a feature of gestational age, or whether they represent specific placental and fetal functional physiological stages [12].

Evidence from the literature indicates that infectious bacteria ascend from the vagina, and that perturbations of the vaginal microbiota, as occurs in bacterial vaginosis, are associated with adverse pregnancy outcomes [38,53]. Cultivation-dependent studies identified members of the genera Prevotella, Bacteroides, Peptostreptococcus, Gardnerella, Mobiluncus and genital mycoplasmas in the placentae of women delivering with or without pre-eclampsia [15,16,19,20,54–57]. DNA-based investigations of the placental microbiota in preterm birth report increased enrichment of Burkholderia sp. and an increased relative abundance of Alphaproteobacteria and Actinomycetaceae and mixed non-cultivable anaerobes [20,21].

Women who deliver preterm with placental evidence of severe chorioamnionitis also demonstrate reduced species diversity within the placental membranes [13]. Chorioamnionitis is associated with a higher abundance of Streptococcus agalactiae, Fusobacterium nucleatum and Ureaplasma parvum [13,15,16,18,20]. High-grade inflammation of the chorionic plate is more frequently associated with specific species including Prevotella bivia, Corinebacterium sp., Escherichia coli, Peptostreptococcus magnus, Streptococcus sp. and the genital mycoplasmas [58]. Polymicrobial infections are a hallmark of chorioamnionitis but it is not entirely clear yet what causes the infiltration by bacteria causing inflammation in the placenta [58].

4.2. Where do placental microorganisms and microbial products in placental pathology arise?

The proposed routes of microbial access to the placenta and amniotic cavity in adverse pregnancy outcomes are the same as those reported for healthy pregnancies. The genital mycoplasmas and Streptococcus agalactiae are frequently isolated bacteria in cases of preterm pre-labor rupture of membranes [59]. However, bacteria isolated from the amniotic cavity are not always recovered from the vagina suggesting an alternate route for microbial translocation [40]. Further, in vitro studies suggest that intact membranes offer a physical barrier to some pathogenic bacteria [60]. Studies assessing the relationship between periodontal disease and preterm birth have produced conflicting results [21,61]. However, fastidious bacteria including Fusobacterium nucleatum of apparently oral cavity origin have been isolated in cases of stillbirth [62].

Interestingly, alterations to the gastrointestinal microbiota, but not the vaginal microbiota have been associated with women who deliver preterm [63]. Specifically, decreased abundance of the genera Clostridium and Bacteroides as measured in stool samples, are known to result in impaired homeostasis [64]. There is evidence for self-modulation between the endogenous microbiota and pathogenic bacteria across multiple anatomical niches. The gastrointestinal and vaginal microenvironments interact due to anatomical location. For example, primary Group B Streptococcus (GBS) carriage is rectal in origin. However, the lactic-acid producing Lactobacillus in the vagina modulate vaginal carriage of GBS [65]. Interestingly, the majority of vaginal lactic acid cannot be produced by human metabolism, highlighting the critical role of the endogenous Lactobacilli in maintaining and modulating homeostasis in the female reproductive tract [66]. Disease previously thought related to the presence of bacteria within the placenta and/or amniotic cavity may actually be the result of dysbiosis in the endogenous microbial community and a resultant loss of protective and homeostatic modulation.

Pathogenic microorganisms in the reproductive tract during pregnancy demonstrate tissue preferences related to adverse pregnancy outcomes. Ureaplasmas and Gardnerella sp. are frequently isolated from the chorioamniontic membranes, whilst Mycoplasma, Leptotrichia, Sneathia and Bergeyella are isolated more frequently from amniotic fluid [18,20,67]. Urinary tract infections during pregnancy have also been associated with microbial alterations resulting in placental enrichment of the genera Streptococcus, Arthrobacter, Klebsiella and Acinetobacter [21]. These genera are frequently encountered in cases of intra-amniotic infection and could potentially colonize the placenta as well.

Furthermore, microbial products including bacterial DNA, which do not necessarily reflect live bacteria, appear sufficient to initiate adverse outcomes in pregnancy. Detection of bacterial DNA from species isolated from the oral cavity has been associated with miscarriage, preterm rupture of membranes, preterm birth, and intrauterine fetal death for the genera Fusobacterium and Streptococcus [62,68].

4.3. How does the placental microbiota precipitate adverse pregnancy outcomes?

The contribution of the placental microbiota in adverse pregnancy outcomes remains to be fully elucidated; however, the production of proinflammatory mediators is a significant mechanism in precipitating preterm birth [69]. Inflammation associated with microbial presence within placental tissue is very likely associated with species-specific virulence factors and host genetics that modulate the host immune response and microbial tissue invasion [55,56,70,71]. Ultimately, variability between host-microbe and microbe-microbe interactions will determine the outcome of microbial presence at this anatomical niche.

The inflammatory response in cases of placental infection frequently travels from the maternal to the fetal tissues with the
maternal immune response detectable prior to the fetal immune response. However, in some cases the fetal response precedes the maternal response, suggesting that the fetal tissue may be the primary site of microbial infiltration [58]. This is further supported by studies reporting dissemination of microbes from distant sites to the placenta and amniotic cavity via the blood supply [72,73].

Cultivation-dependent and independent studies consistently report microbial species present in both healthy term deliveries and pregnancies impacted by adverse outcomes including miscarriage, chorioamnionitis, preterm birth and stillbirth. In addition, there are no clear studies consistently implicating a single species in adverse pregnancy outcomes. Further, in cultivation-dependent studies, microbes were not recovered from a proportion of placentae with high-grade inflammation, perhaps highlighting the limitations of cultivation-dependent studies. All bacteria are not created equal, and there exists significant discordance between cultivation-dependent bacterial identification and clinical pregnancy outcomes [74]. It will be interesting to determine whether this gap is bridged as cultivation-independent techniques become more widely utilized in routine diagnostics [37–40]. Finally, clinical management of infection-related pregnancy morbidity may benefit from knowledge gained as a result of cultivation-independent studies. For example, antibiotic treatment of women diagnosed with BV in early pregnancy, clears the infection but does not reduce significantly antibiotic treatment of women who test negative for BV has been associated with preterm delivery [75]. Understanding the impact of treatment on non-cultivable isolates may improve outcomes in time.

5. Factors changing the placental microbiota

5.1. Maternal obesity

Adverse effects of maternal obesity or excess gestational weight gain have been linked to inflammation in the placenta [76] and anomalies in feto-placental functions [77,78]. While mechanisms are uncertain, new evidence points to the placenta microbiota. In pregnancy, maternal obesity further modifies or amplifies the changes observed in the gut microbiota. These alterations have been shown to affect the development milieu of the offspring [79]. It is unclear if the same phenomenon occurs in the placenta. A recent study [17] evaluated whether obesity or excess gestational weight gain was associated with an altered placental microbiota and if this was more pronounced among women who delivered preterm. At phylum level, prepregnancy obesity and gestational weight gain were not associated with significant differences in the placental microbiota. However, in women with premature deliveries, the placental microbiota was significantly altered by excess gestational weight gain but not by prepregnancy obesity. An increased abundance of Firmicutes, Actinobacteria and decreased Proteobacteria abundance was reported. These results suggest that aberrations in the preterm placental microbiota may be associated with preterm birth. In addition, metagenomic analyses revealed that the placental microbiota in women with preterm birth and excess gestational weight gain had lower expression of genes encoding folate biosynthesis, butanoate metabolism and increased expression of siderophore biosynthesis. These results are tantalizing but do not prove causality.

The origin of the bacteria in the placental microbiota in healthy and unhealthy pregnancies is not fully explored. Three main routes have been proposed: the oral-fetalplacental, gastointestinal-feto-placental and the genitourinary-feto-placental (Fig. 1) [80]. Fetal-placental pregnancy, obesity was associated with dental caries [81], imbalanced oral microflora [82], differences in cervical microflora [83] and profound changes in the gut microbiota [84–87]. Therefore it can be hypothesized that maternal obesity and/or excess gestational weight gain may lead to dysbiosis in the placental microbiota. However this needs to be confirmed.

5.2. Gestational diabetes mellitus (GDM)

GDM is defined as ‘any degree of glucose intolerance with onset or first recognition during pregnancy’ [88] and is associated with multiple adverse maternal and infant outcomes. It has been hypothesized that differences in the placental microbiota could be associated with pregnancy complications (Fig. 2) [57,89] but there is no definitive evidence supporting this hypothesis yet. To date, there is only one study investigating the effect of GDM on the placental microbiota [90], which showed that the placental microbiota from women with diagnosed GDM differed from that of normoglycemic women. GDM women exhibited decreased abundance of the order Pseudomonadales and the genus Acinetobacter. Decreased abundance of Acinetobacter is associated with lower blood eosinophil counts and lower placental expression of numerous anti-inflammatory genes including interleukin (IL)-10. Thus Acinetobacter may have a modulatory effect of the maternal immune system, producing an anti-inflammatory milieu in the placenta. However, no causal relationship can however be inferred from this study due to the cross-sectional design of the study. Maternal exposure to Acinetobacter hofhii in a murine model altered placental Toll-like receptor gene expression and lowered the risk of asthma in the offspring. This provides additional evidence for a potential anti-inflammatory role of this genus in the placenta.

5.3. Probiotics and antibiotics

Human-microbial interaction may occur before birth. In mice, a labeled strain of Enterococcus faecium can cross the placenta into the umbilical cord [46]. In humans, the placenta and meconium of infants have been reported to share some phylotypes [91,92]. Therefore, any microbial supplementation or bacterial suppression during pregnancy may alter the maternal microbiome. Probiotics and antibiotics could potentially alter the composition of the placental microbiota but this has not yet been studied directly. Probiotic interventions have been extensively investigated in relation to systemic inflammation. Maternal oral probiotic supplementation can modulate TLR-related gene expression in the placenta and fetal gut [93]. This means that modulation of the maternal microbiome by probiotics may have an important effect on neonatal intestinal gene expression of immune markers. Moreover, probiotic strains belonging to Bifidobacterium and Lactobacillus have been detected in human placenta [94]. Therefore it has been hypothesized that oral probiotics before and during pregnancy could be an alternative therapy to prevent metabolic diseases in pregnant women at risk [90]. The effect of prebiotic supplementation on the placental microbiota is unknown. Prebiotic foods support beneficial commensals residing in the gut microbiota [95], however whether these effects would extend to the placental microbiota is unclear.

Many pregnant women are exposed to antibiotics during pregnancy or at delivery [96]. Antibiotics cause significant shifts in the gut microbiota resulting in the suppression of both beneficial and pathogenic bacteria [97]. The cause and effect relationship between antibiotic intake and the placental microbiota has not been established. In the largest placental microbiota study to date [21], it was not possible to elucidate whether the placental microbiota was affected by the remote antenatal infection or by antibiotic therapy. Of note, it has been reported that at least 11 types of broad-spectrum antibiotics cross the placenta and reach the fetus [92].
This could potentially alter the first fetal-microbial interactions, which may influence the development of the infant microbiome. Administration of prebiotics/probiotics to pregnant women during pregnancy or labor may help to restore or improve the dysbiotic maternal microbiome.

6. Conclusions

It is clear that the placenta has its own microbiota and its composition is likely to affect pregnancy outcomes. However, since this is a relatively novel area of research, the mechanisms by which this occurs are still unclear. Furthermore, if and how maternal factors including prepregnancy BMI, pre-existing disease as well as pregnancy complications affect the placental microbiota, or the converse, will need to be explored in future studies. A better understanding of the placental microbiota and its role in pregnancy outcomes may contribute to the identification of new therapeutic targets to improve pregnancy outcomes.

Conflict of interest

The authors of this review: ‘Maternal health and the placental microbiome’, Elise S. Pelzer*, Luisa F. Gomez-Arango, Helen L. Barrett and Marloes Dekker Nitert declare no conflicts of interest.

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