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WOMB WITH A VIEW: THE IMPORTANCE OF MATERNAL-FETAL COMMUNICATION DURING EARLY DEVELOPMENT

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OVERVIEW

What is heritability? Is it merely the vertical transfer of your genomic material from egg and sperm? Or is it a far more complex set of traits which arise from the community of genomic and epigenomic material which is vertically transferred during key intervals of development?

The 'Developmental Origins of Health and Disease [DOHaD] Hypothesis' (*Barker*, 1986; *Fleming* et al., 2018) encompasses a substantial body of evidence which temporally and functionally links maternal exposures to adverse outcomes (largely the non-communicable diseases [NCDs]) in her offspring like obesity, metabolic disorders, cardiovascular disease, and behavioural outcomes (see Figure 1 for a schematic overview).

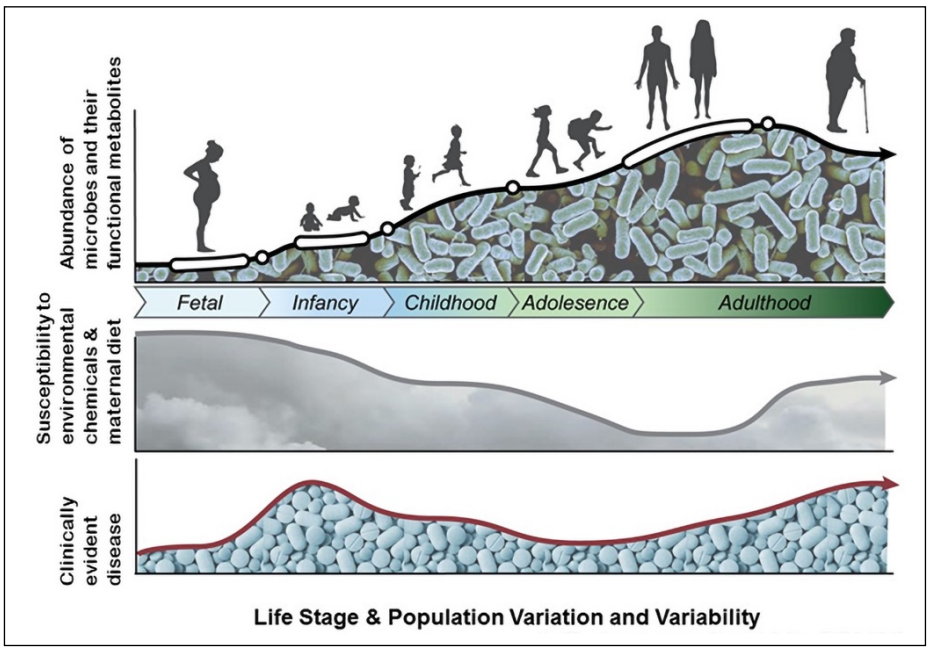

Figure 1: Womb with a view: How do we prepare babies to adapt to the world they are going to be born into? Tolerate commensal microbes and allow colonization? Resist pathogens?
This schematic underlies key questions of our time in microbiome science, and early developmental programming, including foetal development. (Modified from *Aagaard* et al., 2016).

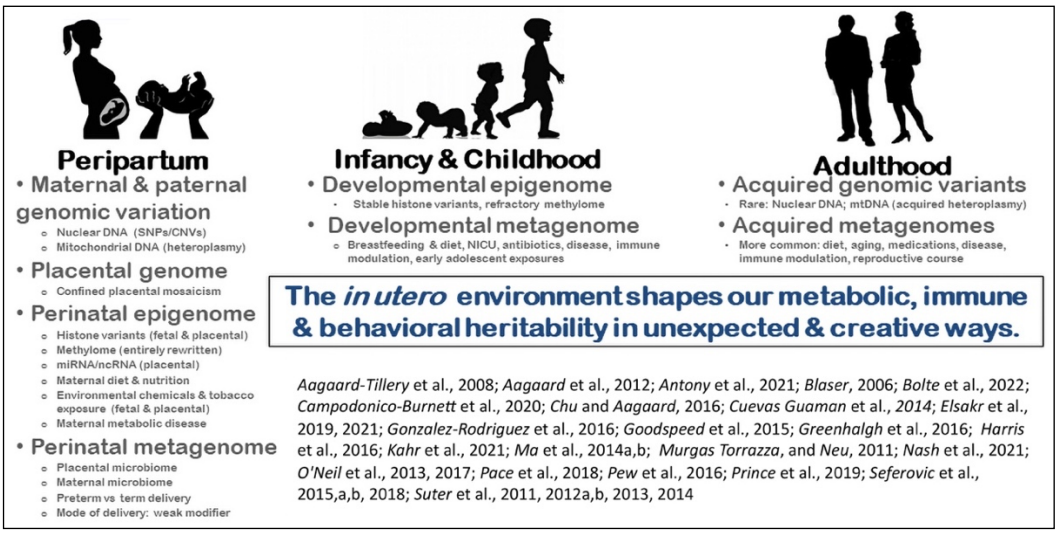

Figure 2: Heritability: What are the molecular mechanisms which facilitate maternal-foetal communication and enable adaptation in a changing world?
This schematic and listed references represent the data from mice to monkeys to humans demonstrating that the majority of our heritable traits are not the product of genomic alleles, but rather epigenomic and metagenomics driven patterning.

Initial mechanistic-minded studies in animal models demonstrated that both maternal nutritional deprivation and a high fat 'Western style' diet feeding brought about meaningful and persistent modulations in postnatal gene expression resulting from epigenomic changes in key metabolic pathways in the offspring (*Aagaard-Tillery* et al., 2008; *Safi-Stibler* and *Gabory*, 2020). More recently, others examined the similar temporal relationships through the lens of microbiome science, leading to the genesis of the 'Hygiene Hypothesis.' The Hygiene Hypothesis suggests that in addition to maternal exposure-driven foetal epigenetic variation, the lack of exposure to microbes early in life predisposes offspring to not only developing these same adverse outcomes, but also atopic and allergic diseases later-in-life (*Blaser*, 2006). However, despite nearly 100 years recognizing these links, we have failed to reveal meaningful mechanistic understandings of 1) how specific maternal elements contribute to functional foetal and early life developmental and 2) how to prevent infant morbidity and mortality. We and others have now spent the last several decades diving into understanding what enables generational adaptation to occur at a far, far more amenable rate than genomic variance and positive selection would allow (*Aagaard-Tillery* et al., 2008; *Aagaard* et al., 2012; *Antony* et al., 2021; *Blaser*, 2006; *Bolte* et al., 2022; *Campodonico-Burnett* et al., 2020; *Chu* and *Aagaard*, 2016; *Cuevas Guaman* et al., *2014*; *Elsakr* et al., 2019, 2021; *Gonzalez-Rodriguez* et al., 2016; *Goodspeed* et al., 2015; *Greenhalgh* et al., 2016; *Harris* et al., 2016; *Kahr* et al., 2021; *Ma* et al., 2014a,b; *Murgas Torrazza*, and *Neu*, 2011; *Nash* et al., 2021; *O'Neil* et al., 2013, 2017; *Pace* et al., 2018; *Pew* et al., 2016; *Prince* et al., 2019; *Seferovic* et al., 2015,a,b, 2018; *Suter* et al., 2011, 2012a,b, 2013, 2014). While Figure 2 depicts a number of mechanisms by which 'heritability' occurs, we focused our discussion at the 2023 Old Herborn University Seminar on the role of the microbiome, its

metagenome, and its accompanying metabolome during key intervals of development (*Aagaard* et al., 2014; *Azad* et al., 2016; *Banerjee* et al., 2020; *Bassols* et al., 2016; *Bolte* et al., 2022; *Butel* et al., 2007; *Chu* and *Aagaard*, 2016; *Chu* et al., 2017; *Claus* et al., 2016; *Collado* et al., 2016; *Gomez-Arango* et al., 2017; *Greenhalgh* et al., 2016; *Doyle* et al., 2014, 2017; *Jasarevic* and *Bale*, 2019; *Liu* et al., 2022; *Ma* et al., 2014a,b; *Nash* et al., 2021; *Pace* et al., 2018, 2021; *Pammi* et al., 2017; *Parnell* et al., 2017; *Prince* et al., 2016, 2019; *Rogier* et al., 2014; *Seferovic* et al., 2015, 2018).

CO-EXISTENCE OF MICROBES AND ANIMALIA SPECIES: HOW ESSENTIAL ARE MICROBES FOR REPRODUCTION AND NORMAL EARLY DEVELOPMENT?

Our laboratory and others have demonstrated that the vaginal, oral and stool microbiota composition and microbiome community function vary during the course of normal pregnancy, thus providing a unique "signature" in pregnancy with relative altered abundance of multiple species and strains (*Aagaard* et al., 2012b; *Butel* et al., 2007; *Chu* et al., 2017; *Liu* et al., 2022; *Ma* et al., 2014a; *Pace* et al., 2021). But what impact does this have on either the pregnancy or the developing infant? Although it has long been suggested that intrauterine infections, such as chorioamnionitis, are the sequelae of ascending microbiota from the upper vagina, we and others have shown that the evidence supporting this notion are relatively sparse and source microbes come from other maternal sites with vertical transfer (both *in* and *ex utero*) or via limited horizontal transfer (*Aagaard* et al., 2014; *Aagaard* and *Hohmann*, 2019; *Azad* et al., 2016; *Banerjee* et al., 2020; *Bassols* et al., 2016; *Bolte* et al., 2022; *Butel* et al., 2007; *Cao* and *Mysorekar*, 2013; *Chen* and *Devaraj*, 2018; *Chen* and *Gur*, 2019; *Chu* et al., 2016, 2017; *Claus* et al., 2016; *Collado* et al., 2016; *Dong* et al., 2015; *Doyle* et al., 2014, 2017; *Goldstein* et al., 2017; *Gomez-Arango* et al., 2017; *Gosalbes* et al., 2013a; *Jasarevic* and *Bale*, 2019; *Kelly* et al., 2021; *Liu* et al., 2022; *Lokugamage* and *Pathberiya*, 2019; *Ma* et al., 2020; *Pace* et al., 2021; *Pammi* et al., 2017; *Parnell* et al., 2017; *Petersen* et al., 2021a, 2021b; *Prince* et al., 2016; *Rogier* et al., 2014; *Roswall* et al., 2021; *Satokari* et al., 2009; *Seferovic* et al., 2019, 2020a,b; *Song* et al., 2021; *Stinson* et al., 2018; *Thaiss* et al., 2016; *Tuominen* et al., 2018; *Zheng* et al., 2015).

Clearly, to exist on Earth is to coexist with microbes. Interactions between microbes and host species within the kingdom Animalia are evident when comparing to their gnotobiotic and/or 'germ free' laboratory derived counterparts. Importantly, germfree derivations of mice, zebrafish, and pigs are capable of survival but are immunologically (*Gensollen* et al., 2016), metabolically (*Cox* et al., 2022), and behaviourally (*Luczynski* et al., 2016) abnormal. Comparing gnotobiotics to naturally-existing Animalia species, which evolved during hundreds of millions of years in a world teeming with microbial communities, it is evident that while survival can occur absent of microbes, normal development is accompanied by immune tolerance to commensal microbes, allowing them to persist while barring highly antigenically and genomically-related pathobionts and pathogens from flourishing.

Indeed, the reliance on microbes for Animalia species fitness is not limited to

immune development. Some animal species, including horses, sheep, and cattle, rely primarily on microbial macromolecules, small molecule intermediates and proteins, and key metabolites as primary sources of dietary energy and micronutrients. Others, like koalas or cuttlefish, have developed highly specific interactions which are hallmark symbiotic characteristics or traits of their species, such as enabling digestion of nutrient-poor food sources (koalas and eucalyptus [*Chong* et al., 2020]) or production of bioluminescence (*McFall-Ngai*, 2014) (cuttlefish). Placental mammals maintain finely tuned relationships with microbial metabolic products, and even seemingly minor disruptions to normal microbial community structure (*e.g*., community dysbiosis) has been associated with the incidence, onset and prevalence of disorders in metabolism and a number of non-communicable diseases in humans and primates (*Girbovan* et al., 2017; *Gosalbes* et al., 2013a; *Huang* et al., 2021; *Moeller* et al., 2018; *van Opstal* and *Bordenstein*, 2015). Although microbial products are capable of influencing foetal development (Figure 1), true vertical transfer requires these microbes be functional, selectable, and capable of colonizing their host during the perinatal window (periconception through early postnatal life). From an ecological perspective, a non-random generational transmission of microbes would provide exclusive opportunities for selection toward host fitness (*Tett* et al., 2019) and limit virulence potential (*Schubbert* et al., 1998). Comprehensive data sources are needed to quantify the contributions of transmission mode toward the acquisition of microbes (*Jiménez* et al., 2008; *Perez* et al., 2007; *Schubbert* et al., 1998; *Tett* et al., 2019) and the mechanisms used to generationally retain them.

WHAT IS THE IMPORTANCE OF MATERNAL-FOETAL COMMUNICATION DURING DEVELOPMENT?

As schematically depicted in Figure 3, there is a fundamental paradox in development: if the womb is sterile and the placenta is a barrier and not a means of communication, how do we tolerate commensal microbes requisite to metabolism, immunity and behaviour and adapt to an ever-changing world? When considering the factors influencing the formation of the foetal microbiome, it is also important to consider how the intrauterine environment itself may influence the microbiota of the developing foetus. Many scientists have challenged the notion of a sterile intrauterine environment in the absence of disease and have purported a distinct placental and amniotic fluid microbiome that is closely similar to the foetal/neonatal microbiome; others argue that any and all representations of microbial content are confounded by contamination (*Aagaard* et al., 2014; *Aagaard* and *Hohmann*, 2019; *Azad* et al., 2016; *Banerjee* et al., 2020; *Bassols* et al., 2016; *Bolte* et al., 2022; *Butel* et al., 2007; *Cao* and *Mysorekar*, 2013; *Chen* and *Devaraj*, 2018; *Chen* and *Gur*, 2019; *Chong* et al., 2020; *Chu* et al., 2016, 2017; *Claus* et al., 2016; *Collado* et al., 2016; *Cox* et al., 2022; *DiGiulio* et al., 2010; *Dong* et al., 2015; *Doyle* et al., 2014, 2017; *Gensollen* et al., 2016; *Girbovan* et al., 2017; *Goldstein* et al., 2017; *Gomez-Arango* et al., 2017; *Gosalbes* et al., 2013a,b; *Hansen* et al., 2015; *Hiltunen* et al., 2021; *Hornef* and *Penders*, 2017; *Huang* et al., 2021; *Jasarevic* and *Bale*, 2019; *Jiménez* et al, 2008; *Kelly* et al., 2021; *Kennedy* et al.,

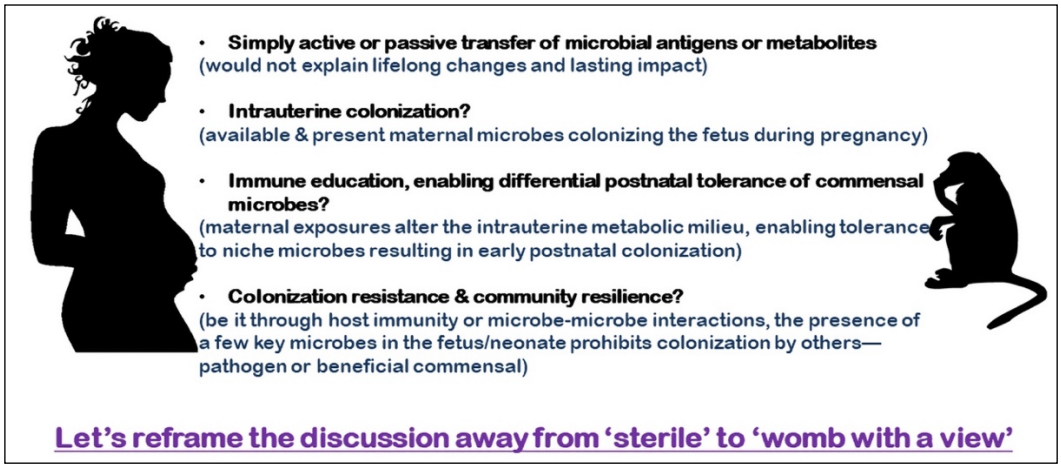

Figure 3: The womb with a view perspective enables us to consider the importance of developing immune tolerance to commensal microbes early in development.
Whether true colonization occurs in utero is yet to be determined, and there is supporting and refuting evidence in both (see the text for references). I remain agnostic as to whether true colonization with live microbes fully occurs in utero. However, what is evident is that microbial products do transfer *in utero* from mother to foetus, inclusive of metagenomic materially, peptidoglycans and other antigens, and microbial metabolites.

2021, 2023; *Liu* et al., 2022; *Lokugamage* and *Pathberiya*, 2019; *Luczynski* et al., 2016; *Ma* et al., 2020; *McFall-Ngai*, 2014; *Mishra* et al., 2021; *Moeller* et al., 2018; *Onderdonk* et al., 2008a; *Pace* et al., 2021; *Pammi* et al., 2017; *Parnell* et al., 2017a,b; *Perez* et al., 2007; *Perez-Muñoz* et al., 2017; *Petersen* et al., 2021a, 2021b; *Prince* et al., 2016; *Rackaityte* et al., 2020; *Rogier* et al., 2014; *Roswall* et al., 2021; *Satokari* et al., 2009; *Schubbert* et al., 1998; *Seferovic* et al., 2019, 2020a,b; *Song* et al., 2021; *Stinson* et al., 2017, 2018; *Tett* et al., 2019; *Thaiss* et al., 2016; *Theis* et al., 2020; *Tuominen* et al., 2018; *van Opstal* and *Bordenstein*, 2015; *Zheng* et al., 2015). Evidence for a unique placental microbiome by virtue of metagenomic characterization stems from a metagenomics study of 320 placentae which demonstrated a low-biomass microbial community of the placental parenchyma and chorionic villi (*Aagaard* et al., 2014). Our study demonstrated a unique placental microbiome niche composed of non-pathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla that was most akin to the human oral microbiome by composition. Other researchers have demonstrated a similarity between the placental microbiota and the neonatal meconium, suggesting that the microbiota may be transferred across the placenta and into the foetus before being excreted into the amniotic fluid as foetal urine; others again argue that these metagenomics signals are largely the result of contamination (*Aagaard* et al., 2014; *Aagaard* and *Hohmann*, 2019; *Bassols* et al., 2016; *Cao* and *Mysorekar*, 2013; *Chen* and *Devaraj*, 2018; *Chen* and *Gur*, 2019; *Chong* et al., 2020; *Collado* et al., 2016; *Cox* et al., 2022; *DiGiulio* et al., 2010; *Dong* et al., 2015; *Doyle* et al., 2014, 2017; *Gensollen* et al., 2016; *Girbovan* et al., 2017; *Goldstein* et al., 2017; *Gomez-Arango* et al., 2017; *Gosalbes* et al., 2013a,b; *Hansen* et al., 2015; *Hiltunen* et al., 2021; *Hornef* and *Penders*, 2017; *Huang* et al., 2021;

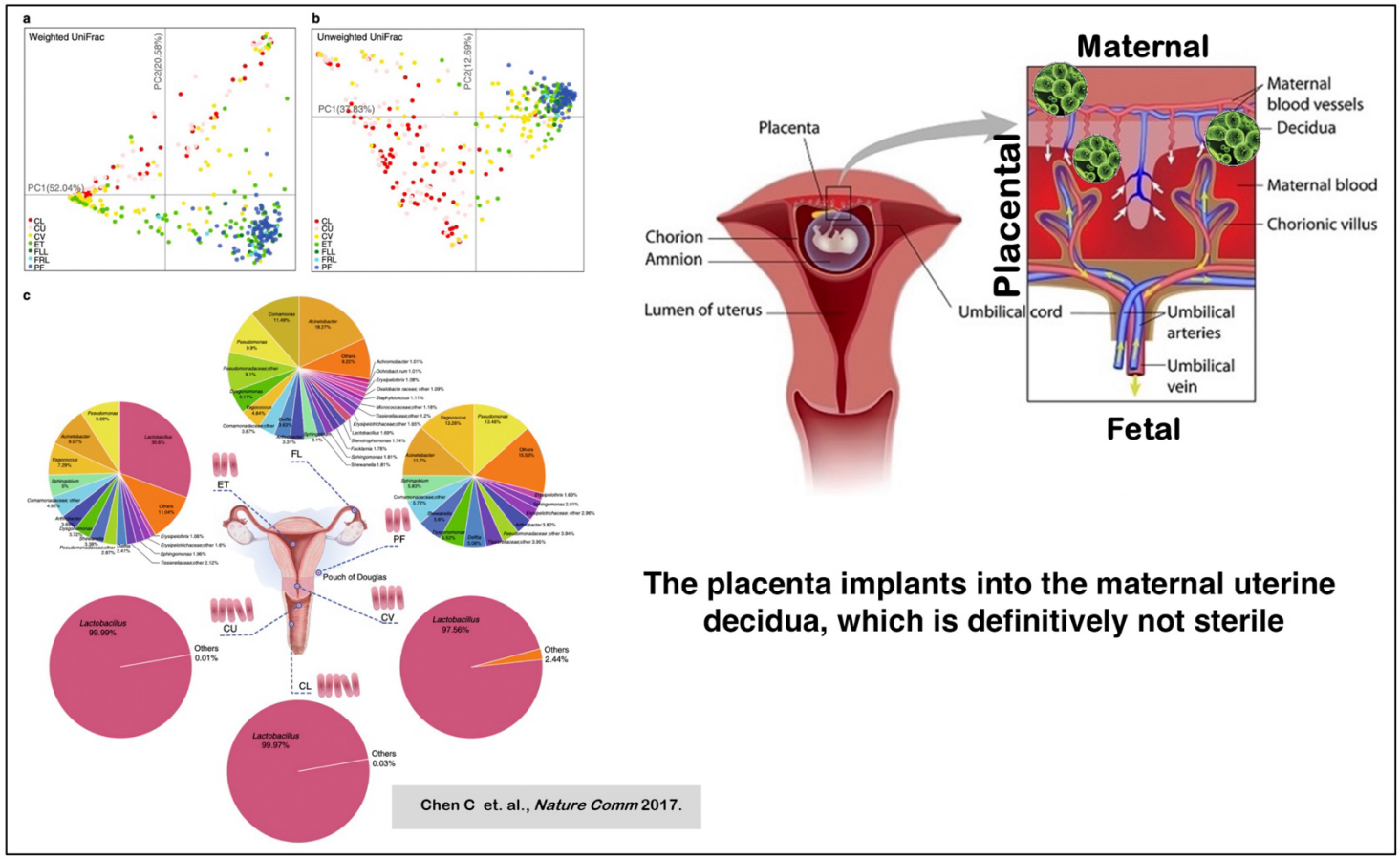

Figure 4: Differing interpretations of highly consistent data: there is a metagenomic signal in amniotic fluid and placenta and the fetus; whether it represents live and persistent microbial colonization *in utero* is yet unclear (see the text for references). The importance of these signals for maternal-fetal communication and fetal adaptation is evident.

Jiménez et al, 2008; *Kelly* et al., 2021; *Kennedy* et al., 2021, 2023; *Lokugamage* and *Pathberiya*, 2019; *Luczynski* et al., 2016; *Ma* et al., 2020; *McFall-Ngai*, 2014; *Mishra* et al., 2021; *Moeller* et al., 2018; *Onderdonk* et al., 2008b; *Parnell* et al., 2017a,b; *Perez* et al., 2007; *Perez-Muñoz* et al., 2017; *Petersen* et al., 2021a, 2021b; *Prince* et al., 2016; *Rackaityte* et al., 2020; *Roswall* et al., 2021; *Satokari* et al., 2009; *Schubbert* et al., 1998; *Seferovic* et al., 2019, 2020a,b; *Song* et al., 2021; *Stinson* et al., 2017, 2018; *Tett* et al., 2019; *Thaiss* et al., 2016; *Theis* et al., 2020; *Tuominen* et al., 2018; *van Opstal* and *Bordenstein*, 2015; *Zheng* et al., 2015). Our publications and those of Gosalbes and colleagues (postulate that because the neonatal meconium microbiota differs from the dominant bacterial groups found in the maternal skin, faecal, and vaginal niches, the neonatal microbiota is unlikely to originate in those maternal locations. Instead, they argue that because meconium is formed starting at mid-gestation in foetal life (17 weeks and beyond), the microbiota detected in meconium is likely not simply due to contact with maternal habitus at time of delivery (*Gosalbes* et al., 2013a). Indeed, it is well established that the meconium expressed within minutes to days of birth has been present in the small bowel since at least 20 weeks of gestation. Chen and Gur hypothesize that maternal comorbidities (including diabetes and hypertension) results in changes in the maternal intestinal, oral, and vaginal microbiomes that facilitate the translocation of bacteria to the intrauterine environment either haematogenously or through direct ascension, suggesting that the placenta is more conduit than barrier (*Chen* and *Gur*, 2019). Recent work from Peterson and colleagues demonstrated that newborns who developed immunoglobulin E (IgE)-mediated allergic sensitization (atopy) by one year of age have a less diverse gut metabolome at birth as measured in the meconium, which begins forming in the foetal gut during the second trimester (Peterson et al., 2021b). They argue that deficiency in microbiota maturation and immune development likely begins in utero rather than at time of delivery.

It is important to acknowledge, however, that there is a debate regarding the existence of a placental/amniotic fluid or foetal microbiome (Figure 4). In our own work, while we have consistently distinguished a metagenomic signal in the placenta from that of contaminant controls, we have also been explicit in noting it to be of low biomass, low abundance, and sparse (*Aagaard* et al., 2014; *Aagaard* and *Hohmann*, 2019; *Azad* et al., 2016; *Banerjee* et al., 2020; *Bolte* et al., 2022; *Butel* et al., 2007; *Chu* et al., 2017; *Claus* et al., 2016; *Goldstein* et al., 2017; *Jasarevic* and *Bale*, 2019; *Liu* et al., 2022; *Ma* et al., 2020, 2014b; *Nash* et al., 2021; *Pace* et al., 2018, 2021; *Pammi* et al., 2017; *Prince* et al., 2019; *Rogier* et al., 2014; *Seferovic* et al., 2015b, 2018, 202b). We have also remained consistently agnostic as to whether the placental or intrauterine microbiome is truly alive and colonizing, with a yet unclear functional role. With further scientific advancement and continued curiosity, we are confident that investigators will determine whether these consistently observed low-biomass communities are alive and colonize the foetus or alternatively enable later colonization through processes of immune tolerance or colonization resistance.

CONCLUSIONS AND CLINICAL SIGNIFICANCE

Here we have described the current state of the science on several aspects of the female reproductive microbiome, as well as their current association with perinatal disorders of both the mother and her offspring. What we understand today is far more complex and confounded than was appreciated less than a decade ago, and is much simpler than what we will come to realize in coming years. The vaginal microbiome varies from one woman to the next, across the lifespan, and in association with both health and disease states. Simplified views that suggest "less diverse and less rich vaginal microbiomes are equivalent to disease states" have been challenged and discounted.

Previously assumed to be "sterile" reproductive tract tissues have been shown to harbour low biomass metagenomes, and yet we remain unclear as to what, how and when the infant is colonized. When we consider species outside humans and mice, the dogma that all foetuses develop in a microbiologically and immunologically naïve environment is not supported by the current published literature. Although the presence of pioneering prenatal microbiota is often considered to be a novel concept, experimental and observational evidence of its existence dates back almost 100 years for many species, including humans. The advent of highly selective cultivation media and concerns regarding contamination-prone nucleic acid sequencing has led to appropriate and necessary questioning of the evidence supporting prenatal exposure to maternal microbiota. Upon comprehensive review of the literature inclusive of heterogenous and orthogonal rigorous methodologies among multiple Animalia species, the state of the science is most consistent with the notion that *in utero* exposure to microbes is sufficient, although not necessary for all species, for normal development when considering heterogeneous cohorts and species on nearly every continent. This robust set of findings may facilitate the transition into a new era pursuing a deeper functional understanding in order to improve the health of humans and animals worldwide.

While we and others have clearly shown that there is, at most, transient differences in the microbiota of neonates born via Caesarean when compared to those born by vaginal delivery, these changes are limited to a few taxa, are not durable, and appear to resolve during infancy. As such, it is not surprising that meaningful lifelong impacts on the development of the metabolic and immune system in mammalian offspring have yet to be causally linked. However, the potential for reduction of harm readily resides within our reach if we can reduce the disparities that contribute to increased Caesarean delivery risk. For example, with a lens on our diabetic or obese population, based on multiple lines of evidence, we can confidently anticipate three benefits of widened availability of optimized nutrition with relief of food scarcity and unrestricted access to medical care both preconception and prenatally. We would (1) improve glycaemic control, optimizing foetal growth, (2) lower the Caesarean delivery rate and increase the duration of human milk feeding, and (3) potentially mitigate the longer-term risks from exposure to these conditions *in utero*. This heightened attention to maternal perinatal health - like improved glucose control and appropriate weight gain - can be attained with widened access to clinical and public health interventions and patient counselling without incurring any additional risk to mom or foetus. While there are many outstanding questions regarding

the neonatal and infant microbiome, we caution that societal focus needs to shift away from a narrow focus on reducing Caesarean delivery rates to meet a certain quota - which as we have demonstrated may be difficult to achieve in today's society - to optimizing maternal healthcare before, during, and after pregnancy. Additionally, efforts to restore the neonatal and infant microbiomes with vaginal or faecal seeding may fail to yield beneficial outcomes and may be harmful at both individual and broader societal levels. As physicians, our first responsibility is to do no harm. Despite growing popularity of neonatal seeding in the general press, health care practitioners and patients should only perform seeding practices within the confounds of strict scientific protocols to ensure safety. To ultimately improve maternal and neonatal outcomes in association with presumptively beneficial alterations in the microbiome, attention should be directed to established beneficial realms of improved access and availability of preconception and prenatal care, nutritional counselling, lactation services, and limiting food scarcity and other health disparities.

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LITERATURE

Aagaard-Tillery, K.M., Grove, K., Bishop, J., Ke, X., Fu, Q., McKnight, R., Lane, R.H.: Developmental origins of disease and determinants of chromatin structure: maternal diet modifies the primate fetal epigenome. J. Mol. Endocrinol. 41, 91-102 (2008).

Aagaard, K., Riehle, K., Ma, J., Segata, N., Mistretta, T.-A., Coarfa, C., Raza, S., Rosenbaum, S., Van den Veyver, I., Milosavljevic, A., Gevers, D., Huttenhower, C., Petrosino, J., and Versalovic, J.:. A metagenomic approach to characterization of the vaginal microbiome signature in pregnancy. PLoS One **7**, e36466 (2012b).

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

Aagaard, K., Stewart, C.J., and Chu, D.: Una destinatio, viae diversae: Does exposure to the vaginal microbiota confer health benefits to the infant, and does lack of exposure confer disease risk? EMBO Rep. 17, 1679-1684 (2016).

Aagaard, K. and Hohmann, E.: Regulating microbiome manipulation. Nat. Med. 25, 874-876 (2019).

Antony, K.M., Romezi, M., Lindgren, K., Mitchell, K.B., Venable, S.F., Racusin, D.A., Suter, M.A., and Aagaard, K.M.: Maternal Metabolic Biomarkers are Associated with Obesity and Excess Gestational Weight Gain. Am. J. Perinatol. 38(S 01), e173-e181 (2021).

Azad, M.B., Konya, T., Persaud, R.R., Guttman, D.S., Chari, R.S., Field, C.J., Sears, M.R., Mandhane, P.J., Turvey, S.E., Subbarao, P., Becker, A.B., Scott, J.A., and Kozyrskyj, A.L.; CHILD Study Investigators: Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. BJOG 123, 983-993 (2016).

Banerjee, S., Suter, M.A., and Aagaard, K.M.: Interactions between Environmental Exposures and the Microbiome: Implications for Fetal Programming. Curr. Opin. Endocr. Metab. Res. 13, 39-48 (2020).

Barker, D.: Infant mortality, childhood nutrition, and ischaemic heart disease in england and wales. Lancet 327, 1077-1081 (1986).

Bassols, J., Serino, M., Carreras-Badosa, G., Burcelin, R., Blasco-Baque, V., Lopez-Bermejo, A., and Fernandez-Real, J.-M.: Gestational diabetes is associated with changes in placental microbiota and microbiome. Pediatr. Res. 80, 777-784 (2016).

Blaser, M.J.: Who are we? Indigenous microbes

and the ecology of human diseases. EMBO Rep. 7, 956-960 (2006).

Bolte, E.E., Moorshead, D., and Aagaard, K.M.: Maternal and early life exposures and their potential to influence development of the microbiome. Genome Med. 14, 4 (2022).

Butel, M.-J., Suau, A., Campeotto, F., Magne, F., Aires, J., Ferraris, L., Kalach, N., Leroux, B., and Dupont, C.: Conditions of bifidobacterial colonization in preterm infants: a prospective analysis. J. Pediatr. Gastroenterol. Nutr. 44, 577-582 (2007).

Campodonico-Burnett, W., Hetrick, B., Wesolowski, S.R., Schenk, S., Takahashi, D.L., Dean, T.A., Sullivan, E.L., Kievit, P., Gannon, M., Aagaard, K., Friedman, J.E., and McCurdy, C.E.: Maternal Obesity and Western-Style Diet Impair Fetal and Juvenile Offspring Skeletal Muscle Insulin-Stimulated Glucose Transport in Nonhuman Primates. Diabetes 69, 1389-1400 (2020).

Cao, B. and Mysorekar, I.U.: Intracellular bacteria in placental basal plate localize to extravillous trophoblasts. Placenta 35, 139-142 (2013).

Chen, C., Song, X., Wei, W., Zhong, H., Dai, J., Lan, Z., Li, F., Yu, X., Feng, Q., Wang, Z., Xie, H., Chen, X., Zeng, C., Wen, B., Zeng, L., Du, H., Tang, H., Xu, C., Xia, Y., Xia, H., Yang, H., Wang, J., Wang, J., Madsen, L., Brix, S., Kristiansen, K., Xu, X., Li, J., Wu, R., and Jia, HJ.: The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat. Commun. 8, 875 (2017).

Chen, H.J. and Gur, T.L.: Intrauterine Microbiota: Missing, or the Missing Link? Trends Neurosci. 42, 402-413 (2019)

Chen, X. and Devaraj, S.: Gut Microbiome in Obesity, Metabolic Syndrome, and Diabetes. Curr. Diab. Rep. 18, 129 (2018).

Chong, R., Cheng, Y., Hogg, C.J., and Belov, K.: Marsupial gut microbiome. Front. Microbiol. 11, 1058 (2020).

Chu, D.M. and Aagaard, K.M.: Microbiome: Eating for trillions. Nature 532 316-317 (2016).

Chu, D.M., Ma, J., Prince , A.L., Antony, K.M., Seferovic, M.D., and Aagaard, K.M.: Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery. Nat. Med. 23, 314-326 (2017).

Claus, S.P., Guillou, H., and Ellero-Simatos, S.: The gut microbiota: a major player in the toxicity of environmental pollutants? NPJ Biofilms Microbiomes 2, 16003 (2016).

Collado, M.C., Rautava, S., Aakko, J., Isolauri, E., and Salminen, S.: Human gut colonisation may be initiated in utero by distinct microbial communities in the placenta and amniotic fluid. Sci. Rep. 6, 23129 (2016).

Cox, T.O., Lundgren, P., Nath, K., and Thaiss, C.A.: Metabolic control by the microbiome. Genome Med. 14, 80 (2022).

Cuevas Guaman, M., Sbrana, E., Shope, C., Showalter, L., Hu, M., Meloche, S., and Aagaard, K.: Administration of antenatal glucocorticoids and postnatal surfactant ameliorates respiratory distress syndrome–associated neonatal lethality in Erk3−/− mouse pups. Pediatr. Res. 76, 24-32 (2014).

DiGiulio, D.B., Romero, R., Amogen, H.P., Kusanovic, J.P., Bik, E.M., Gotsch, F., Kim, C.J., Erez, O., Edwin, S., and Relman, D.A.: Microbial prevalence, diversity and abundance in amniotic fluid during preterm labor: A molecular and culture-based investigation. PLoS One 3, e3056 (2008).

DiGiulio, D.B., Romero, R., Kusanovic, J.P., Gómez, R., Kim, C.J., Seok, K.S., Gotsch, F., Mazaki-Tovi, S., Vaisbuch, E., Sanders, K., Bik, E.M., Chaiworapongsa, T., Oyarzún, E., and Relman, D.A.: Prevalence and diversity of microbes in the amniotic fluid, the fetal immune response, and pregnancy outcome in women with preterm prelabor rupture of membranes. Am. J. Reprod. Immunol. 64, 38-57 (2010).

Dong, X.-D., Li, X.-R., Luan, J.-J. Liu, X.-F., Peng, J., Luo, Y.-Y., and Liu, C.-J.: Bacterial communities in neonatal feces are similar to mothers' placentae. Can. J. Infect. Dis. Med. Microbiol. 26, 90-94 (2015).

Doyle, R.M., Alber, D.G., Jones, H.E., Harris, K., Fitzgerald, F., Peebles, D., and Klein, N.: Term and preterm labour are associated with distinct microbial community structures in placental membranes which are independent of mode of delivery. Placenta 35, 1099-1101 (2014).

Doyle, R.M., Harris, K., Kamiza, S., Harjunmaa, U., Ashorn, U., Nkhoma, M., Dewey, K.G., Maleta, K., Ashorn, P., and Klein, N.:

Bacterial communities found in placental tissues are associated with severe chorioamnionitis and adverse birth outcomes. PLoS One 12, e0180167 (2017).

Elsakr, J.M., Dunn, J.C., Tennant, K., Zhao, S.K., Kroeten, K., Pasek, R.C., Takahashi, D.L., Dean, T.A., Velez Edwards, D.R., McCurdy, C.E., Aagaard, K.M., Powers, A.C., Friedman, J.E., Kievit, P., and Gannon, M: Maternal Western-style diet affects offspring islet composition and function in a non-human primate model of maternal over-nutrition. Mol. Metab. 25, 73-82 (2019).

Elsakr, J.M., Zhao, S.K., Ricciardi, V., Dean, T.A., Takahashi, D.L., Sullivan, E., Wesolowski, S.R., McCurdy, C.E., Kievit, P., Friedman, J.E., Aagaard, K.M., Edwards, D.R.V., Gannon, and M.: Western-style diet consumption impairs maternal insulin sensitivity and glucose metabolism during pregnancy in a Japanese macaque model. Sci. Rep. 11, 12977 (2021).

Fleming, T.P., Watkins, A.J., Velazquez, M.A., Mathers, J.C., Prentice, A.M., Stephenson, J., Barker, M., Saffery, R., Yajnik, C.S., Eckert, J.J., Hanson, M.A., Forrester, T., Gluckman, P.D., and Godfrey, K.M.: Origins of lifetime health around the time of conception: causes and consequences. Lancet 391, 1842-1852 (2018).

Gensollen, T., Iyer, S.S., Kasper, D.L., and Blumberg, R.S.: How colonization by microbiota in early life shapes the immune system. Science 352, 539-544 (2016).

Girbovan, A., Sur, G., Samasca, G., and Lupan, I.: Dysbiosis a risk factor for celiac disease. Med. Microbiol. Immunol. 206, 83-91 (2017).

Goldstein, R.F., Abell, S.K., Ranasinha, S., Misso, M., Boyle, J.A., Black, M.H., Li, N., Hu, G., Corrado, F., Rode, L., Kim, Y.J., Haugen, M., Song, W.O., Kim, M.H., Bogaerts, A., Devlieger, R., Chung, J.H., and Teede, H.J.: Association of Gestational Weight Gain With Maternal and Infant Outcomes: A Systematic Review and Meta-analysis. JAMA 317, 2207-2225 (2017).

Gomez-Arango, L.F., Barrett, H.L., McIntyre, H.D., Callaway, L.K., Morrison, M., and Dekker Nitert, M.: Contributions of the maternal oral and gut microbiome to placental microbial colonization in overweight and obese pregnant women. Sci. Rep. 7, 2860 (2017).

Gonzalez-Rodriguez, P., Cantu, J., O'Neil, D., Seferovic, M.D., Goodspeed, D.M., Suter, M.A., and Aagaard, K.M.: Alterations in expression of imprinted genes from the H19/IGF2 loci in a multigenerational model of intrauterine growth restriction (IUGR). Am. J. Obstet. Gynecol. 214, 625.e1-625.e11 (2016).

Goodspeed, D., Seferovic, M.D., Holland, W., Mcknight, R.A., Summers, S.A., Branch, D.W., Lane, R.H., and Aagaard, K.M.: Essential nutrient supplementation prevents heritable metabolic disease in multigenerational intrauterine growth-restricted rats. FASEB J. 29, 807-819 2015.

Gosalbes, M.J., Llop, S., Vallès, Y., Moya, A., Ballester, F., and Francino, M.P.: Meconium microbiota types dominated by lactic acid or enteric bacteria are differentially associated with maternal eczema and respiratory problems in infants. Clin. Exp. Allergy 43, 198-211 (2013a).

Gosalbes, M.J., Llop, S., Vallès, Y., Moya, A., Ballester, F., and Francino, M.P.: Meconium microbiota types dominated by lactic acid or enteric bacteria are differentially associated with maternal eczema and respiratory problems in infants. Clin. Exp. Allergy 43, 198-211 (2013b).

Greenhalgh, K., Meyer, K.M., Aagaard, K.M., and Wilmes, P.: The human gut microbiome in health: establishment and resilience of microbiota over a lifetime. Environ. Microbiol. 18, 2103-2116 (2016).

Hansen, R., Scott, .KP., Kha,n S., Martin, J.C., Berry, S.H., Stevenson, M., Okpapi, A., Munro, M.J., and Hold, G.L.: First-pass meconium samples from healthy term vaginally-delivered neonates: an analysis of the microbiota. PLoS One 10, e0133320 (2015).

Harris, R.A., Alcott, C.E., Sullivan, E.L., Takahashi, D., McCurdy, C.E., Comstock, S., Baquero, K., Blundell, P., Frias, A.E., Kahr, M., Suter, M., Wesolowski, S., Friedman, J.E., Grove, K.L., and Aagaard, K.M.: Genomic Variants Associated with Resistance to High Fat Diet Induced Obesity in a Primate Model. Sci. Re. 6, 36123 (2016).

Hiltunen, H., Hanani, H., Luoto, R., Turjeman, S., Ziv, O., Isolauri, E., Salminen, S., Koren, O., and Rautava, S.: Preterm infant meconium microbiota transplant induces growth failure, inflammatory activation, and metabolic disturbances in germ-free mice. Cell Rep. Med. 2, 100447 (2021).

Hornef, M. and Penders, J.: Does a prenatal bacterial microbiota exist? Mucosal Immunol. 10, 598-601 (2017).

Huang, Y., Liao, J., Liu, X., Zhong, Y., Cai, X., and Long, L.: Review: The role of intestinal dysbiosis in Parkinson's disease. Front. Cell. Infect. Microbiol. 11, 615075 (2021).

Jašarević, E. and Bale, T.L.: Prenatal and postnatal contributions of the maternal microbiome on offspring programming. Front. Neuroendocrinol. 55, 100797 (2019).

Jiménez, E., Marín, M.L., Martín, R., Odriozola, J.M., Olivares, M., Xaus, J., Fernández, L., and Rodríguez, J.M.: Is meconium from healthy newborns actually sterile? Res. Microbiol. 159, 187-193 (2008).

Kahr, M.K., Antony, K.M., Galindo, M., Whitham, M., Hu, M., Aagaard, K.M., and Suter, M.A.: SERUM GLP-2 is Increased in Association with Excess Gestational Weight Gain. Am. J. Perinatol. 40, 400-406 (2021).

Kelly, J.C., Nolan, L.S., and Good, M.: Vaginal seeding after cesarean birth: Can we build a better infant microbiome? Med 2, 889-891(2021).

Kennedy, K.M., Gerlach, M.J., Adam, T., Heimesaat, M.M., Rossi, L., Surette, M.G., Sloboda, D.M., and Braun, T.: Fetal meconium does not have a detectable microbiota before birth. Nat. Microbiol. 6, 865-873 (2021).

Kennedy, K.M., de Goffau, M.C., Perez-Muñoz, M.E., Arrieta, M.-C., Bäckhed, F., Bork, P., Braun, T., Bushman, F.D., Dore, J., de Vos, W.M., Earl, A.M., Eisen, J.A., Elovitz, M.A., Ganal-Vonarburg, S.C., Gänzle, M.G., Garrett, W.S., Hall, L.J., Hornef, M.W., Huttenhower, C., Konnikova, L., Lebeer, S., Macpherson, A.J., Massey, R.C., McHardy, A.C., Koren, O., Lawley, T.D., Ley, R.E., O'Mahony, L., O'Toole, P.W., Pamer, E.G., Parkhill, J., Raes, J., Tarrei, T., Salonen, A., Segal, E., Segata, N., Shanahan, F., Sloboda, D.M., Smith, G.C.S,. Sokol, J., Spector, T.D., Surette, M.G., Tannock, G.W., Walker, A.W., Yassour, M., and Walter, J.: Questioning the fetal microbiome illustrates pitfalls of low-biomass microbial studies. Nature 613, 639-649 (2023).

Liu, Y., Elworth, R.L., Jochum, M.D., Aagaard, K.M., and Treangen, T.J.: De novo identification of microbial contaminants in low microbial biomass microbiomes with Squeegee. Nat. Commun. 13, 6799 (2022).

Lokugamage, A.U. and Pathberiya, S.D.C.: The microbiome seeding debate - let's frame it around women-centred care. Reprod. Health 16, 91 (2019).

Luczynski, P., McVey Neufeld, K.-A., Oriach, C.S., Clarke, G., Dinan, T.G., and Cryan, J.F.: Growing up in a bubble: Using germ-free animals to assess the influence of the gut microbiota on brain and behavior. Int. J. Neuropsychopharmacol. 19, pyw020 (2016).

Ma, J., Coarfa, C., Qin, X., Bonnen, P.E., Milosavljevic, A., Versalovic, J., and Aagaard, K.: mtDNA haplogroup and single nucleotide polymorphisms structure human microbiome communities. BMC Genomics 15, 257 (2014a).

Ma, J., Prince, A.L., Bader, D., Hu, M., Ganu, R., Baquero, K., Blundell, P., Alan Harris, R., Frias, A.E., Grove, K.L., and Aagaard, K.M.: High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. Nat. Commun. 5, 3889 (2014b).

Ma, J., Qiao, Y., Zhao, P., Li, W., Katzmarzyk, P.T., Chaput, J.-P., Fogelholm, M., Kuriyan, R., Lambert, E.V., Maher, C., Maia, J., Matsudo, V., Olds, T., Onywera, V., Sarmiento, O.L., Standage, M., Tremblay, M.S., Tudor-Locke, C., and Hu, G.; ISCOLE Research Group: Breastfeeding and childhood obesity: A 12-country study. Matern. Child Nutr. 16, e12984 (2020).

McFall-Ngai, M.J.: The importance of microbes in animal development: Lessons from the squid-vibrio symbiosis. Annu. Rev. Microbiol. 68, 177-194 (2014).

Mishra, A., Lai, G.C., Yao, L.J., Aung, T.T., Shentel, N., Rotter-Maskowitz, A., Sheperdson, E., Singh, G.S.N., Pai, R., Shanti, A., Wong, R.M.M., Lee, A., Khyriem, C., Dutertre, C.A., Chakarov, S., Srinivasan, K.G., Shadan, N.B., Zhang, X.-

M., Khalilnezhad, S., Cottier, F., Tan, A.S.M., Low, G., Chen, P., Fan, Y., Hor, P.X., Lee, A.K.M., Choolani, M., Vermijlen, D., Sharma, A., Fuks, F., Straussman, R., Pavelka, N., Malleret, B., McGovern, N., Albani, S., Chan, J.K.Y., and Ginhoux, F.: Microbial exposure during early human development primes fetal immune cells. Cell 184:3394-3409.e20 (2021).

Moeller, A.H., Suzuki, T.A., Phifer-Rixey, M., and Nachman, M.W.: Transmission modes of the mammalian gut microbiota. Science 362, 453-457 (2018).

Murgas Torrazza, R. and Neu, J.: The developing intestinal microbiome and its relationship to health and disease in the neonate. J. Perinatol. 31, Suppl. 1., S29-S34 (2011)

Nash, M.J., Dobrinskikh, E., Newsom, S.A., Messaoudi, I., Janssen, R.C., Aagaard, K.M., McCurdy, C.E., Gannon, M., Kievit, P., Friedman, J.E., and Wesolowski, S.R.: Maternal Western diet exposure increases periportal fibrosis beginning in utero in non-human primate offspring. JCI Insight 6, e154093 (2021).

Onderdonk, A.B., Delaney, M..L, DuBois, A.M., Allred, N., and Leviton, A.: Detection of bacteria in placental tissues obtained from extremely low gestational age neonates. Am. J. Obstet. Gynecol. 198, 110.e1-110.e7 (2008a).

Onderdonk, A.B., Hect, J.L., McElrath, T.F., Delaney, M.L., Allred, E.N., and Leviton, A.: Colonization of second-trimester placenta parenchyma. Am. J. Obstet. Gynecol. 199, 52.e1-52.e10 (2008b).

O'Neil, D., Mendez-Figueroa, H., Mistretta, T.A., Su, C., Lane, R.H., and Aagaard, K.M.: Dysregulation of Npas2 leads to altered metabolic pathways in a murine knockout model. Mol. Genet. Metab. 110, 378-387 (2013).

O'Neil, D.S., Stewart, C.J., Chu, D.M., Goodspeed, D.M., Gonzalez-Rodriguez, P.J., Shope, C.D., and Aagaard, K.M.: Conditional postnatal deletion of the neonatal murine hepatic circadian gene, Npas2, alters the gut microbiome following restricted feeding. Am. J. Obstet. Gynecol. 217, 218.e1-218.e15 (2017).

Pace, R.M., Prince, A.L., Ma, J., Belfort, B.D.W., Harvey, A.S., Hu, M., Baquero, K., Blundell, P., Takahashi, D., Dean, T., Kievit, P., Sullivan, E.L., Friedman, J.E., Grove, K., and Aagaard, K.M.: Modulations in the offspring gut microbiome are refractory to postnatal synbiotic supplementation among juvenile primates. BMC Microbiol. 18, 28 (2018).

Pace, R.M., Chu, D.M., Prince, A.L., Ma, J., Seferovic, M.D., and Aagaard, K.M.: Complex species and strain ecology of the vaginal microbiome from pregnancy to postpartum and association with preterm birth. Med. 2, 1027-1049 (2021).

Pammi, M., Cope, J., Tarr, P.I., Warner, B.B., Morrow, A.L., Mai, V., Gregory, K.E., Kroll, J.S., McMurtry, V., Ferris, M.J., Engstrand, L., Engstrand Lilja , H., Hollister, E.B., Versalovic, J., and Neu, J.: Intestinal dysbiosis in preterm infants preceding necrotizing enterocolitis: a systematic review and meta-analysis. Microbiome 5, 31 (2017).

Parnell, L.A., Briggs, C.M., Cao, B., Delannoy-Bruno, O., Schrieffer, A.E., and Mysorekar, I.U.: Microbial communities in placentas from term normal pregnancy exhibit spatially variable profiles. Sci. Rep. 7, 11200 (2017a).

Parnell, L.A., Brigs, C.M., Cao, B., Belannoy-Bruno, O., Schrieffer, A.E., and Mysorekar, I.U.: Microbial communities in placentas from term normal pregnancy exhibit spatially variable profiles. Sci. Rep. 7, 11200 (2017b).

Perez, P.F., Doré, J., Leclerc, M., Levenez, F., Benyacoub, J., Serrant, P., Segura-Roggero, I., Schiffrin, E.J., and Donnet-Hughes, A.: Bacterial imprinting of the neonatal immune system: lessons from maternal cells? Pediatrics 119, e724-e732 (2007).

Perez-Muñoz, M.E., Arrieta, M.-C., Ramer-Tai,t, A.E., and Walter, J.: A critical assessment of the “sterile womb” and “in utero colonization” hypotheses: implications for research on the pioneer infant microbiome. Microbiome 5, 48 (2017).

Petersen, C., Dai, D.L.Y., Boutin, R.C.T., Sbihi, H., Sears, M.R., Moraes, T.J., Becker, A.B., Azad, M.B., Mandhane, P.J., Subbarao, P., Turvey, S.E., and Finlay, B.B.: A rich meconium metabolome in human infants is associated with early-life gut microbiota compo-

sition and reduced allergic sensitization. Cell. Rep. Med. 2, 100260 (2021a).

Petersen, C., Dai, D.L.Y., Boutin, R.C.T., Sbihi, H., Sears, M.R., Moraes, T.J., Becker, A.B., Azad, M.B., Mandhane, P.J., Subbarao, P., Turvey, S.RE., and Finlay, B.B.: A rich meconium metabolome in human infants is associated with early-life gut microbiota composition and reduced allergic sensitization. Cell. Rep. Med. 2, 100260 (2021b).

Pew, B.K., Harris, R.A., Sbrana, E., Guaman, M.C., Shope, C., Chen, R., Meloche, S., and Aagaard, K.: Structural and transcriptomic response to antenatal corticosteroids in an Erk3-null mouse model of respiratory distress. Am. J. Obstet. Gynecol. 215, 384.e1-384.e89 (2016).

Prince, A.L., Ma, J., Kannan, P.S., Alvarez, M., Gisslen, T., Harris, R.A., Sweeney, E.L., Knox, C.L., Lambers, D.S., Jobe, A.H., Chougnet, C.A., Kallapur, S.G., and Aagaard, K.M.: The placental membrane microbiome is altered among subjects with spontaneous preterm birth with and without chorioamnionitis. Am. J. Obstet. Gynecol. 214, 627.e1-627.e16 (2016).

Prince, A.L., Pace, R.M., Dean, T., Takahashi, D., Kievit, P., Friedman, J.E., and Aagaard, K.M. :The development and ecology of the Japanese macaque gut microbiome from weaning to early adolescence in association with diet. Am. J. Primatol. 81, e22980 (2019).

Rackaityte, E., Halkias, J., Fukui, E.M., Mendoza, V.F., Hayzelden, C., Crawford, E.D., Fujimura, K.E., Burt, T.D., and Lynch, S.V.: Viable bacterial colonization is highly limited in the human intestine in utero. Nat. Med. 26, 599-607 (2020).

Rogier, E.W., Frantz, A.L., Bruno, M.E.C., Wedlund, L., Cohen, D.A., Stromberg, A.J., and Kaetzel, C.S.: Secretory antibodies in breast milk promote long-term intestinal homeostasis by regulating the gut microbiota and host gene expression. Proc. Natl. Acad. Sci. USA 111, 3074-3079 (2014).

Roswall, J., Olsson, L.M., Kovatcheva-Datchary, P., Nilsson, S., Tremaroli, V., Simon, M.-C., Kiilerich, P., Akrami, R., Krämer, M., Uhlén, M., Gummesson, A., Kristiansen, K., Dahlgren, J., and Bäckhed, F.: Developmental trajectory of the healthy human gut microbiota during the first 5 years of life. Cell Host Microbe 29, 765-776 (2021).

Safi-Stibler, S. and Gabory, A.: Epigenetics and the Developmental Origins of Health and Disease: Parental environment signalling to the epigenome, critical time windows and sculpting the adult phenotype. Semin. Cell Dev. Biol. 97, 172-180 (2020).

Satokari, R., Grönroos, T., Laitinen, K., Salminen, S., and Isolauri, E.: Bifidobacterium and Lactobacillus DNA in the human placenta. Lett. Appl. Microbiol. 48, 8-12 (2009).

Schubbert R, Hohlweg U, Renz D, Doerfler W. On the fate of orally ingested foreign DNA in mice: chromosomal association and placental transmission to the fetus. Mol. Gen. Genet. 1998;259:569-76.

Seferovic, M.D., Goodspeed, D.M. Chu, D.M., Krannich, L.A., Gonzalez-Rodriguez, P.J., Cox, J.E. and Aagaard, K.M.: Heritable IUGR and adult metabolic syndrome are reversible and associated with alterations in the metabolome following dietary supplementation of 1-carbon intermediates. FASEB J. 2640-4652 (2015a).

Seferovic, M.D., Goodspeed, D.M., Chu, D.M., Krannich, L.A., Gonzalez-Rodriguez, P.J., Cox, J.E., and Aagaard, K.M.: Heritable IUGR and adult metabolic syndrome are reversible and associated with alterations in the metabolome following dietary supplementation of 1-carbon intermediates. FASEB J. 29, 2640-2652 (2015b).

Seferovic, M.D., Beamish, C.A., Mosser, R.E., Townsend, S.E., Pappan, K., Poitout, V., Aagaard, K.M., and Gannon, M.: Increases in bioactive lipids accompany early metabolic changes associated with beta-cell expansion in response to short-term high-fat diet. Am. J. Physiol. Endocrinol. Metab. 315, E1251-E1263 (2018).

Seferovic, M.D., Pace, R.M., Carroll, M., Belfort, B., Major, A.M., Chu, D.M., Racusin, D.A., Castro, E.C.C., Muldrew, K.L., Versalovic, J., and Aagaard, K.M.: Visualization of microbes by 16S in situ hybridization in term and preterm placentas without intraamniotic infection. Am. J. Obstet. Gynecol. 221, 146.e1-146.e23 (2019).

Seferovic, M.D., Mohammad, M., Pace, R.M., Engevik, M., Versalovic, J., Bode, L., Haymond, M., and Aagaard, K.M.: Maternal diet alters human milk oligosaccharide composition with implications for the milk metagenome. Sci. Rep. 10, 22092 (2020a).

Seferovic, M.D., Mohammad, M., Pace, R.M., Engevik, M., Versalovic, J., Bode, L., Haymond, M., and Aagaard, K.M.: Maternal diet alters human milk oligosaccharide composition with implications for the milk metagenome. Sci. Rep. 10, 22092 (2020b).

Song, S.J., Wang, J., Martino, C., Jiang, L., Thompson, W.K., Shenhav, L., McDonald, D., Marotz, C., Harris, P.R., Hernandez, C.D., Henderson, N., Ackley, E., Nardella, D., Gillihan, C., Montacuti, V., Schweizer, W., Jay, M., Combellick, J., Sun, H., Garcia-Mantrana, I., Raga, F.G., Collado, M.C., Rivera-Viñas, J.I., Campos-Rivera, M., Ruiz-Calderon, J.F., Knight, R., and Dominguez-Bello, M.G.: Naturalization of the microbiota developmental trajectory of Cesarean-born neonates after vaginal seeding. Med. 2, 951-964 (2021).

Stinson, L.F., Payne, M.S., and Keelan, J.A.: Planting the seed: Origins, composition, and postnatal health significance of the fetal gastrointestinal microbiota. Crit. Rev. Microbiol. 43, 352-369 (2017).

Stinson, L.F., Payne, M.S., and Keelan, J.A.: A Critical Review of the Bacterial Baptism Hypothesis and the Impact of Cesarean Delivery on the Infant Microbiome. Front. Med. (Lausanne) 5, 135 (2018).

Suter, M., Bocock, P., Showalter, L., Hu, M., Shope, C., McKnight, R., Grove, K., Lane, R., and Aagaard-Tillery, K.: Epigenomics: maternal high-fat diet exposure in utero disrupts peripheral circadian gene expression in nonhuman primates. FASEB J. 25, 714-726 (2011).

Suter, M.A., Chen, A., Burdine, M.S., Choudhury, M., Harris, R.A., Lane, R.H., Friedman, J.E., Grove, K.L., Tackett, A.J., and Aagaard, K.M.: A maternal high-fat diet modulates fetal SIRT1 histone and protein deacetylase activity in nonhuman primates. FASEB J. 26, 5106-5114 (2012a).

Suter, M.A., Sangi-Haghpeykar, H., Showalter, L., Shope, C., Hu, M., Brown, K., Williams, S., Harris, R.A., Grove, K.L., Lane, R.H., and Aagaard, K.M.: Maternal high-fat diet modulates the fetal thyroid axis and thyroid gene expression in a nonhuman primate model. Mol. Endocrinol. 26, 2071-2080 (2012b).

Suter, M.A., Takahashi, D., Grove, K.L., and Aagaard, K.M.: Postweaning exposure to a high-fat diet is associated with alterations to the hepatic histone code in Japanese macaques. Pediatr. Res. 74, 252-258 (2013).

Suter, M.A., Ma, J., Vuguin, P.M., Hartil, K., Fiallo, A., Harris, R.A., Charron, M.J., and Aagaard, K.M.: In utero exposure to a maternal high-fat diet alters the epigenetic histone code in a murine model. Am. J. Obstet. Gynecol. 210, 463.e1-463.e11 (2014).

Tett, A,, Huang, K.D., Asnicar, F., Fehlner-Peach, H., Pasolli, E., Karcher, N., Armanini, F., Manghi, P., Bonham, K., Zolfo, M., De Filippis, F., Magnabosco, C., Bonneau, R., Lusingu, J., Amuasi, J., Reinhard, K., Rattei, T., Boulund, F., Engstrand, L., Zink, A., Collado, M.C., Littman, D.R., Eibach, D., Ercolini, D., Rota-Stabelli, O., Huttenhower, C., Maixner, F., and Segata, N.. The Prevotella copri complex comprises four distinct clades underrepresented in westernized populations. Cell Host Microbe 26, 666–679 (2019).

Thaiss, C.A., Zmora, N., Levy, M., and Elinav, E.: The microbiome and innate immunity. Nature 535, 65-74 (2016).

Theis, K.R., Romero, R., Winters, A.D., Jobe, A.H., Gomez-Lopez, N., and Young, V.B.: Lack of evidence for microbiota in the placental and fetal tissues of Rhesus macaques. mSphere 5, e00210-e00220 (2020).

Tuominen, H., Rautava, S., Syrjänen, S., Collado, M.C., and Rautava, J.: HPV infection and bacterial microbiota in the placenta, uterine cervix and oral mucosa. Sci. Rep. 8, 9787 (2018).

van Opstal, E.J. and Bordenstein, S.R.: Rethinking heritability of the microbiome. Science 349, 1172-1173 (2015).

Zheng, J., Xiao, X., Zhang, Q., Mao, L., Yu, M., and Xu, J.: The Placental Microbiome Varies in Association with Low Birth Weight in Full-Term Neonates. Nutrients 7, 6924-6937 (2015).