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The placental exposome, placental epigenetic adaptations and lifelong cardio-metabolic health

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A B S T R A C T

The placental exposome represents the sum of all placental exposures, and through its influence on placental function can affect an individual's susceptibility to cardio-metabolic disease later in life. The placental exposome includes direct exposures during gestation, as well as those prior to gestation that affect the gametes or aspects of maternal physiology that influence placental function. This review will discuss the evidence for placental responses to environmental signals and its involvement in programming offspring health. A wide range of exposures may influence the placenta including maternal metabolic and endocrine status, nutrition, stress and toxins. Epigenetic changes within the placenta induced by these exposures may mediate persistent effects on placental function. Identifying which exposures are most influential in terms of placental function and offspring health is key to focusing future research and developing stratified and personalised interventions.

1. Introduction

Placental function supports fetal development and builds the foundations for lifelong cardio-metabolic health. The placenta is a fetal organ at the interface between the fetus and the mother and provides the fetus with nutrients, removes toxins and has a role in protecting the fetus from external influences. The ability of the placenta to carry out these functions depends on the interplay between gene expression and the placental exposome, the sum of all placental exposures (Lewis et al., 2012). If placental function is compromised, this can lead to developmental trade-offs, reducing the physiological resilience of the offspring and increasing susceptibility to disease in later life (see Fig. 1).

This review will discuss the placental responses to environmental exposures, whether they are pre- or peri-conceptional, or act at later stages of gestation, which could subsequently influence fetal development. Epidemiological studies identified the initial associations between maternal exposures, the placenta and fetal programming. Where possible this review will focus primarily on human data, introducing data from animal models as necessary to supplement gaps in the human data. Placental structure and function will be discussed in order to understand how the placenta adapts to translate signals from the maternal environment and influence fetal development. In addition, we will review the maternal and environmental factors that influence the placenta, evidence for placental involvement in programming offspring health, together with the role of epigenetic mechanisms in contributing to these events.

1.1. The placenta and fetal programming of cardio-metabolic health in later life

An individual's risk of developing chronic disease in adult life is in part determined by how they developed *in utero* (Hanson and Gluckman, 2014). Epidemiological studies show associations between the *in utero* environment, as represented by birth weight, and cardio-metabolic health in later life (Barker et al., 1989). These studies are supported by animal models that are helping to elucidate the mechanisms underlying these associations, which include changes in epigenetic markers (Christoforou and Sferruzzi-Perri, 2020). As the placenta is a central determinant of fetal development, its structure and function may have long-term influences on health (Burton et al., 2016). As a selective barrier to the maternal environment and gatekeeper to the supply of oxygen and nutrients, placental structure and function are responsible for providing the resources to support appropriate fetal development. Where adequate nutrients are not provided, the resulting developmental compromises may lead to the programming of postnatal cardio-metabolic health.

Demonstrating the role of the placenta in human population studies is complicated by the difficulties of assessing placental function *in utero*. As a result, most studies have focused on birth weight, a surrogate indicator of the intrauterine environment and of the placenta's ability to support fetal development. Large epidemiological studies report that a higher placental to birth weight ratio is associated with postnatal cardiovascular disease; including coronary heart disease and higher systolic

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blood pressure (Hemachandra et al., 2006; Risnes et al., 2009; Wen et al., 2011). These findings suggest the fetus has not grown to its optimum size despite having an appropriately sized placenta and suggest that there may be maternal or external environmental exposures that influence how the placenta functions and supports the developing fetus. In addition, placental size and shape are associated with postnatal hypertension in a sex specific manner (Eriksson et al., 2010).

Knockout mouse models show associations between an abnormal placental phenotype and embryonic defects in the heart and vascular system, which supports the idea of a placental-heart axis during development (Perez-Garcia et al., 2018). Changes to utero-placental hemodynamics influence the blood flow to and from the fetus and can alter normal development of the fetal heart and circulation (Linask et al., 2014). As development of the placenta and heart occurs at similar times in gestation and both rely on common nutrients and genes, any alterations to these factors may influence both organs (Cohen et al., 2021). Interactions between the placenta and the fetal cardiovascular system may therefore help elucidate how placental insufficiency has long-lasting effects on cardiovascular health (Matthiesen et al., 2016).

2. Placental determinants of fetal programming

2.1. Placental structure

The placenta originates from the embryonic trophectoderm and develops over the course of gestation to meet increasing fetal requirements. Placental development is described elsewhere (Turco and Moffett, 2019) but in brief, following implantation, in the first trimester placental villi form and become vascularized. Maternal blood flow starts around 12 weeks of gestation, before which the fetus is nourished by histotrophic secretions from endocrine glands. In the second trimester the villi, now in direct contact with maternal blood, grow and branch, increasing the surface area available for exchange. The placental villi therefore provide a physical barrier between the maternal circulation and their core of fetal blood vessels. The layers of the barrier include a multinucleate syncytiotrophoblast in direct contact with maternal blood, a discontinuous layer of cytotrophoblast cells, then the connective tissue and the fetal capillary endothelium. In the third trimester, the villi stop growing but assume a more mature form with terminal capillaries in close association with the syncytiotrophoblast thus reducing diffusion distance between maternal and fetal blood.

The placenta responds to a wide range of exposures including maternal metabolic and endocrine status, nutrition, stress and toxins by altering its structure and function, which can influence fetal resource supply and thereby fetal growth and the subsequent effects on lifelong cardio-metabolic health (Sferruzzi-Perri and Camm, 2016). Exposures that affect the early development of the placenta may have persistent effects across the remainder of gestation. For instance, disruptions in placental development in the first or second trimester can reduce the number or branching of the villi. Reducing villous number can reduce the size of exchange area, limiting the capacity for nutrient and waste transfer. Smaller placentas are associated with smaller babies, suggesting exchange area is a determinant of fetal growth. In addition, impaired vascularisation of the placental villi can increase placental vascular resistance and increase the demands on the fetal heart. This may manifest clinically as growth-restricted fetuses with absent or reversed end diastolic umbilical flow, which may have long-term consequences (Mayhew et al., 2004).

2.2. Placental function

To support fetal development the placenta must provide maternal nutrients to the fetus and clear waste products from the fetal blood. Understanding how these placental functions are affected by *in utero* exposures is necessary to understand how they could influence fetal development and ultimately mediate long-term effects on cardiovascular health.

2.2.1. Placental nutrient transport

The placenta is responsible for transporting both macro and micronutrients to the fetus. There is clear evidence that the processes mediating the transfer of these nutrients is regulated by maternal signals.

Placental amino acid transport is affected by maternal hormone, nutritional and endocrine signals as well as by fetal growth promoting signals. Signals of low maternal resources decrease placental amino acid transport, whereas signals of maternal resource abundance increase placental amino acid transport to optimize fetal fitness (Vaughan et al., 2017). In maternal nutrient restriction, impaired placental amino acid transporter expression and activity is associated with fetal growth restriction (Cetin, 2003; Jansson et al., 2002). Rodent models of maternal dietary restriction demonstrate that the decreased placental transport precedes the fetal growth restriction as an adaptation to match fetal growth to the environment and enhance survival (Jansson et al., 2006a). These models result in compensatory responses such as changes to

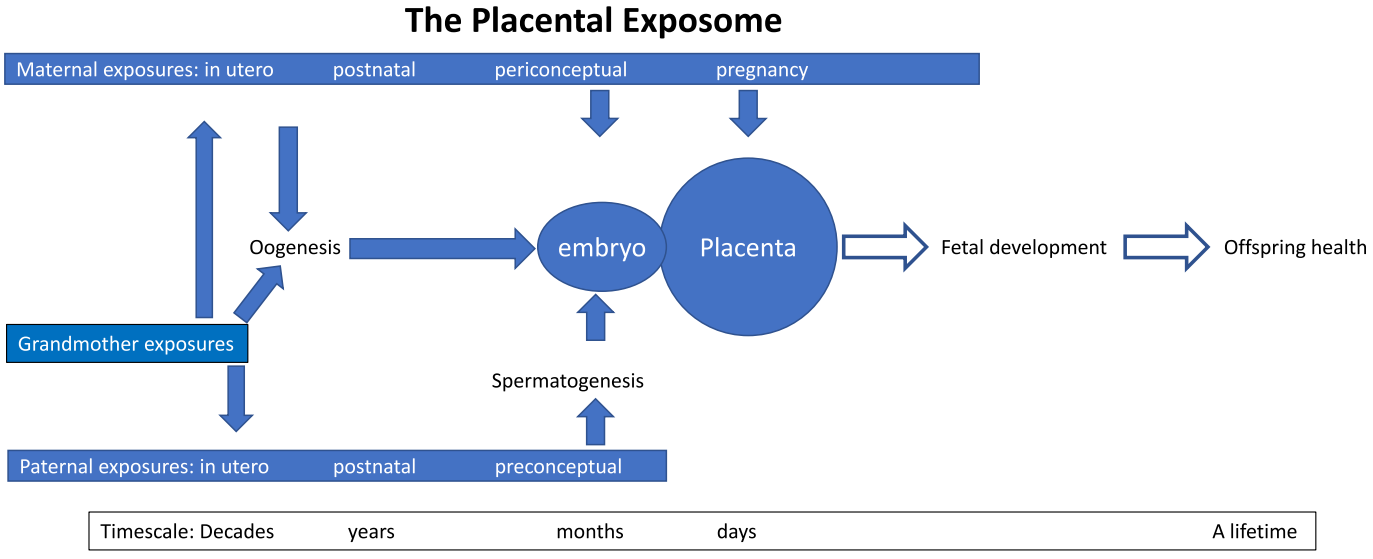

Fig. 1. The placental exposome is the sum of exposures, which may have occurred over many decades. Pre-pregnant exposures may by mediated via epigenetic marks on the gametes or via exposures that influence maternal body composition.

placental transport capacity and placental efficiency to protect development, they are also associated with adult offspring cardiovascular, metabolic and behavioural dysfunction (Caetano et al., 2021).

Specific membrane transporters are up-regulated in placentas from pregnancies with gestational diabetes mellitus (GDM), including those for amino acids (Vaughan et al., 2017), fatty acids (Segura et al., 2017) and glucose (Stanirowski et al., 2018). Altered placenta function may therefore underlie the abnormal fetal growth observed in this disorder (Jansson et al., 2006b) and the associated range of cardio-metabolic disorders seen in offspring of obese and/or GDM mothers that include obesity and type 2 diabetes (Gallo et al., 2017).

The pregnancy complication preeclampsia is also associated with altered placental membrane transporters, specifically the aquaporins (AQPs), which transport water and small uncharged molecules across cell membranes. The human placenta expresses several aquaporins in a special and temporal manner and these play key roles in maternal-fetal fluid balance (Escobar et al., 2012). Disruption of maternal-fetal fluid exchange may result in abortion, premature birth, malformation and fetal growth restriction. In placentas from pregnancies with pre-eclampsia there is altered expression of the aquaporins AQP3 and AQP9, implicating placental water, urea, and glycerol transport in this disorder (Pérez-Pérez et al., 2020). Placental function may therefore underlie the associations between maternal hypertension disorders, fetal growth restriction and effects on the blood pressure of the children (Falkner, 2020).

2.2.2. The renin angiotensin system (RAS) and placental function

Maternal and fetal circulating and tissue renin-angiotensin systems (RASs) play key roles in pregnancy, regulating maternal blood pressure and fluid volume, promoting placentation and regulating uteroplacental blood flow (Pringle et al., 2011; Ito et al., 2002; Valdés et al., 2013). Dysregulation of this endocrine system therefore affects placental function and may contribute to cardiovascular effects in the offspring.

Angiotensin (ANG) II causes vasoconstriction within the feto-placental vasculature and activation of this system can increase perfusion pressure and potentially place stress on the fetal heart (Lofthouse et al., 2019). ANG II acts via the AT1 and AT2 receptors, with AT1 present in the syncytiotrophoblast and AT2 predominantly in the fetus. Angiotensin-converting enzyme 2 (ACE2) within the placenta converts ANG II to Ang-(1–7), in order to protect against the oxidative stress, inflammation and vasoconstrictior effects of ANG II (Santos et al., 2003; Tallant et al., 2005; Khajah et al., 2016; Simões e Silva et al., 2013).

A potential imbalance in the two opposing RAS pathways, favouring the ANG II/AT1R pathway is observed in the placentas of women with preeclampsia and fetal growth restriction along with reduced ACE2 expression (Tamanna et al., 2020). Furthermore, reduced placental expression of Ace2 following maternal protein restriction may contribute to the fetal growth restriction and associated adulthood hypertension observed in rats (Gao et al., 2012). As the drugs that target the ANG II/AT1R pathway cannot be given in pregnancy, the protective ACE2/Ang-(1–7)/MasR arm could be a target for therapeutic intervention (Tamanna et al., 2021).

2.2.3. Effects of the placenta on early life microbiome

The gut microbiome is important for nutrient synthesis and absorption, immunological roles and growth and development. Disturbances to the early gut microbiome are thought to contribute to adverse health outcomes later in life including obesity, diabetes and allergic disease (Butel et al., 2018; Young, 2012). There is evidence that birth mode can influence the early-life gut microbial composition (Kapourchali and Cresci, 2020), however whether the placenta plays a direct role in the development of the neonatal gut microbiome is unclear. While some researchers identify a placental microbiome and suggest transfer of maternal bacteria to the fetus (Collado et al., 2016; Aagaard et al., 2014; Satokari et al., 2009), other researchers have suggested that when contamination is accounted for no placental microbiome can be detected (Olomu et al., 2020).

However, the placenta may also have indirect effects on neonatal gut colonisation via its effects on gut development and maturation for instance via fetal exposure to glucocorticoids. The composition and activity of bacteria in the early life gut may be modulated by the maternal environment potentially via the placenta and this could programme poor cardio-metabolic health. Infants from overweight mothers are born with so-called obesogenic gut microbes, increased risk of postnatal obesity and a reduced community of bacteria that contribute to energy regulation and metabolic signalling (Tun et al., 2018; Mueller et al., 2016). Further work is required to determine the placenta's role in fetal microbial colonization.

2.3. Epigenetic mechanisms in the placenta

Epigenetic regulation plays an important role in determining placental function. Exposures which affect placental epigenetic mechanisms are likely to be key determinants of programming effects on the fetus. Epigenetic mechanisms include both DNA methylation within gene regulatory regions and histone modifications that control the packaging of DNA (Januar et al., 2015). Epigenetic modifications within the placenta can be demonstrated in response to environmental exposures and where these affect placental function may lead to dysregulation of normal development or epigenetic programming in the fetus.

Critical windows for establishing the epigenetic profile occur during gametogenesis and in the preimplantation embryo, with DNA demethylation and re-methylation resulting in lower methylation in trophoblast-derived cells (Reik et al., 2001). The placental exposome therefore includes exposures that occur during gestation, as well as those that occur before or around conception. Examples of pre-conceptional exposure are factors that affect gametogenesis as well as the mother's physiology and anatomy in ways that influence placental development or function. For instance, the grandmother's diet may affect epigenetic markers within the oocytes developing in her fetus's ovary, which could go on to affect placental function in her daughter's pregnancy many years later. DNA methylation also regulates genes involved in trophoblast migration and invasion that establishes embryo implantation and form the placenta (Rahnama et al., 2006).

The human placenta has a unique epigenetic profile of low global DNA methylation (Gama-Sosa et al., 1983) with specific epigenetic marks that could make them more susceptible to environmental programming. The placenta also expresses imprinted genes, which are linked to fetal growth alterations (St-Pierre et al., 2012). Imprinted genes are expressed in a parent-of-origin manner, with their DNA methylation profile established in the germ cell and protected from the early methylation remodelling (Reik et al., 2001). Disruption of the methylation levels of genomic imprinting regions potentially due to environmental stressors can have major consequences on both fetal and placental development.

Maternal factors such as nutrition (Heijmans et al., 2008), obesity (Hoyo et al., 2012), depression and anxiety (Oberlander et al., 2008) or smoking (Suter et al., 2010) during pregnancy have been shown to influence placental epigenetic mechanisms. Placental DNA methylation levels may also change over the course of gestation suggesting potential for further modification by environmental factors (Simner et al., 2017). As the epigenome regulates placental development and function, any alterations could affect subsequent fetal development (Novakovic and Saffery, 2012). In humans increased global placental DNA methylation is associated with being born large for gestational age (Dwi Putra et al., 2020) and increased or decreased methylation of specific genes occurs in placentas from both small and large for gestational age babies, both factors associated with increased risk of adulthood cardio-metabolic disease (Banister et al., 2011; Filiberto et al., 2011). How the placenta responds to its exposome may also depend on the sex of the fetus, for example the placentas of female fetuses are more sensitive to glucocorticoid levels in humans (Stark et al., 2009), possibly due to sex

differences in placental glucocorticoid receptor expression (Saif et al., 2014). This may in part be mediated by sex DNA that is observed within the placenta (Andrews et al., 2021).

Although it is difficult to determine causality in human studies, associations between placental DNA methylation and fetal growth suggest that the outcome of altered placental DNA methylation or factors affecting placental DNA methylation affect fetal growth, which is a risk factor for postnatal cardio-metabolic disease. Studies in rodent dietary restriction models suggest reduced placental size is accompanied by altered DNA methylation of placental genes associated with fetal growth restriction (Reamon-Buettner et al., 2014). This rodent model also induces changes in gene expression and DNA methylation in the offspring, including those related to growth and metabolism (Gong et al., 2010), and is known to induce cardiovascular and metabolic dysfunction in the adult offspring. The changes observed in the placenta may therefore be adaptive mechanisms aimed at protecting the fetus from an adverse environment, but at the risk of programming later disease.

3. Effects of exposures on the placenta

The placenta may be able to fully or partially protect the fetus from certain exposures, reducing their impact on the fetus and its postnatal health, but there will be other exposures from which the placenta cannot protect the fetus. To understand the role of the placental in protecting fetal development, and thus the foundations for lifelong cardio-metabolic health, it is necessary to have a better understanding of what exposures affect the placenta, which have the greatest impact, and the potential mechanisms involved.

Environmental exposures may occur in the pre-conceptional period, for example affecting gametogenesis, around the time of conception, or throughout gestation, via changes in the uterine environment or maternal biology (Fleming et al., 2018). Changes in placental structure, growth, and function induced by a sub-optimal maternal environment may affect placental nutrient transfer to the fetus and the release of placental molecules into the maternal and fetal circulation (Jansson and Powell, 2013). The placenta perceives the maternal environmental via signals from the maternal circulation, although the identity of these signals remains unclear. Proposed candidates include glucocorticoids and IGFs, which could be representative of the maternal nutritional status. Indeed, changes in placental growth and nutrient transfer capacity, with associated effects on fetal growth, can be observed in response to environmental signals such as mTor, hormones, or IGF2 (Diaz et al., 2014; Constância et al., 2002).

A better understanding of the effects of environmental exposures on the placenta will help to identify appropriate and timely interventions to optimise placental function and offspring cardio-metabolic health.

3.1. Pre- and peri-conceptional exposures

The pre or peri-conceptional period has been show to significantly impact offspring health with cardiovascular, metabolic and behavioural effects on adult offspring (Fleming et al., 2018). Pre-conceptional influences can span generations via effects on gametogenesis *in utero*. The peri-conceptional period covers oocyte meiotic maturation, spermatozoa differentiation, fertilisation and mitotic cell cycles in the zygote and the onset of morphogenesis up to implantation. Although the placenta does not form until after implantation, pre- or peri-conceptual exposures may still have effects on placental structure and function.

3.1.1. Oocytes and sperm

The ovarian reserve of primordial follicle oocytes, which make the lifetime supply of oocytes, form during fetal life while a woman is in her mother's womb, meaning the grandmother's environment can affect the egg that makes the grandchild. Indeed, maternal low-protein diet is associated with low ovarian reserve in mouse offspring (Winship et al., 2018). *In vitro* studies of bovine and murine oocyte maturation indicate that this early nutritional environment can reduce oocyte development with alterations to the blastocyst transcriptome and epigenome and altered metabolism in the embryos (Sunde et al., 2016). Adult males produce sperm continuously and the epigenetic programming of these sperm may reflect their current environment. This is reflected in mouse studies that show effects of paternal and grand-paternal factors such as obesity and diet on offspring health (Cropley et al., 2016; Watkins et al., 2018). These paternal signals may be transmitted via sperm quality and epigenetic status and seminal fluid effects on the uterine environment, with corresponding effects on the placenta (Cropley et al., 2016; Watkins et al., 2018).

3.1.2. Peri-conceptional uterine environment

Data from mouse studies suggests maternal environment in the peri-conceptual period may influence the embryo and subsequent placentation. A preimplantation maternal low protein diet influences trophectoderm cell proliferation and spreading, correlating with increased risk of postnatal cardiovascular dysfunction (Eckert et al., 2012). This is thought to be via mTOR signalling acting as a sensor for maternal nutrient levels. This has the potential to reduce the effectiveness of the trophectoderm in mediating invasion of the maternal endometrium and alter the trajectory of placental development. In sheep, pre-implantation progesterone treatment can alter placental amino acid transporter expression and fetal amino acid levels in the third trimester (Halloran et al., 2021). Progesterone's effects on the uterine epithelium are likely to have influenced how the placenta developed. This provides an example of how the interplay between maternal and fetal exposures can have long-term effects across gestation.

In conceptions achieved using assisted reproductive technologies, where *in vitro* manipulations are implemented during times of epigenetic reprogramming, changes in epigenetic regulation in mammalian gametes and embryos are observed (Rivera, 2019). This has implications for the placenta, since assisted reproductive technologies may induce altered DNA methylation in embryonic tissues which form the placenta. Effects on the imprinted genes, known to be highly expressed in placenta and to regulate growth (e.g. the IGF2/H19 locus) may be a particular concern here (Turan et al., 2010; Chen et al., 2010). People born following assisted reproductive technologies show increased prevalence of altered DNA methylation resulting in imprinting disorders, which have adverse clinical features associated with growth, development, and metabolism (Lazaraviciute et al., 2014). The effects of assisted reproductive technologies on the placenta are also seen in rodents, where embryo culture (early nutritional exposures) can disrupt allele-specific expression of imprinted genes such as the H19/IGF2 locus, along with aberrant embryonic, placental and fetal DNA methylation patterns (Rivera et al., 2008). Specifically, a reduction in methionine can alter DNA methylation in bovine embryo culture, again including imprinted genes linked to fetal over-growth (Clare et al., 2021).

3.1.3. Pre-gestational maternal factors

Many factors which affect the placenta during gestation have their origin in the mother's health and body composition. These factors may reflect past maternal environment, such as her diet, exercise levels and exposure to environmental toxins. Maternal body mass index (BMI) is a consequence of past diet and activity and has been shown to affect placental function (Hirschmugl et al., 2017), while maternal obesity induces effects on oocyte metabolism (Leary et al., 2015). Maternal muscle mass, also linked to diet and activity, may affect the activity of placental amino acid transporters (Lewis et al., 2010).

Given that placental function can be influenced by environmental exposures even before pregnancy is established, interventions to improve placental function in the pre-gestational period may be the most effective.

3.2. Maternal metabolic and endocrine environment during pregnancy

The effects of metabolic and endocrine status in pregnancy are most obviously illustrated by maternal diabetes and obesity, however studies suggesting muscle mass also influences placental function suggest more subtle influences are also at play. While past maternal nutrition will be reflected in maternal body composition, nutrient availability during pregnancy can also affect the placenta's ability to deliver nutrients to the fetus.

3.2.1. Maternal diabetes and obesity

Maternal diabetes is associated with poor infant and maternal outcomes, in particular the development of fetal macrosomia. Neonates from mothers with diabetes have increased adipose tissue and may be predisposed to obesity in later life, creating a lifelong health burden and perpetuating intergenerational cycles of disease (Feig et al., 2017). While there is clearly an association between poor maternal glycaemic control, as determined by HbA_{1c}, and macrosomia, the association is complicated (Feig et al., 2017). Higher rates of macrosomia are also found in women with diabetes using insulin pumps, which typically improves glycaemic control, and in women with a high BMI (Kallas--Koeman et al., 2014). It is clear that additional factors beyond maternal glucose levels must be important, and we propose that differences in placental glucose transfer capacity may explain this complexity (Day et al., 2013).

Offspring are also at increased risk of developing obesity and other metabolic complications in later life if exposed to maternal obesity (Maffeis and Morandi, 2017). Although there are clear relationships between maternal obesity or diabetes and fetal adiposity, the underlying mechanisms are unclear. It is likely that the placenta responds to signals in the intrauterine environment by altering function such as glucose and lipid transport or by increasing growth and therefore its functional capacity. Increased fetal growth could therefore be due to maternal obesity or weight gain in pregnancy affecting placental size (Diouf et al., 2014) (Swanson and Bewtra, 2008). Membrane transporter abundance or activity in the placenta could also be regulated by nutritional and endocrine signals reflecting the maternal body composition or metabolic status (Lewis et al., 2013). Corresponding changes to the pattern of expression and DNA methylation of placental glucose transporters across gestation implicate epigenetics as a potential mechanism regulating these transport processes (Novakovic et al., 2013).

3.2.2. Maternal diet

Studies in humans and animal models suggest that macro and micro nutrient composition of the maternal diet during pregnancy can have long-term postnatal consequences in the offspring (Christoforou and Sferruzzi-Perri, 2020; Stephenson et al., 2018). Maternal diet can affect placental structure (Jansson et al., 2006a; Lewis et al., 2001) and human placental growth can be influenced by maternal nutrient restriction or periods of fasting during pregnancy (Alwasel et al., 2010; van Abeelen et al., 2011). Some effects of maternal diet are dependent on fetal sex, as are the associations between placental shape and hypertension in the offspring (van Abeelen et al., 2011; Alwasel et al., 2014). Maternal over-nutrition also has sex-specific placental effects, influencing placental weight in rats (Vickers et al., 2011). These findings suggest that placental responses to maternal environmental exposures are involved in the sex differences in the fetal programming of lifelong cardio-metabolic health.

Nutrient availability can also regulate placental nutrient transport, both due to nutrient availability and in response to placental sensing of maternal nutrient levels. For instance amino acid levels are sensed by the mTOR system which in turn regulates amino acid transporter levels and is linked to fetal growth restriction (Roos et al., 2005, 2009). Placental amino acids transport capacity decreases before the onset of fetal growth restriction (Jansson et al., 2006a) suggesting that the placenta alters its function in response to the maternal environment in order to match fetal growth to the prevailing environment. Reducing the demands of the fetus in periods of undernutrition, for example, may maintain the pregnancy, but may come at the expense of adverse long-term consequences induced by growth restriction that include obesity, diabetes and cardiovascular disease.

Micronutrient undernutrition during gestation includes deficiency of minerals and vitamins, such as zinc, iron, calcium, vitamin A, and vitamin D, which are essentially for biochemical and metabolic processes. Micronutrients are important for epigenetic regulation as they are involved in methylation reactions and contribute to DNA and histone modifying enzymes (DNA methyltransferases, histone lysine methyltransferases and histone deacetylases enzymes). For example, zinc deficiency during gestation contributes to the programming of several chronic diseases in adult life, such as atherosclerosis and related vascular diseases, congestive heart failure, coronary heart disease, renal insufficiency, hypertension, diabetes (Tomat et al., 2011), effects which may be mediated by epigenetic modifications.

Vitamin D deficiency is common during pregnancy and is associated with maternal preeclampsia and gestational diabetes, which influence the risk of cardio-metabolic disease in the offspring (Ideraabdullah et al., 2019). Vitamin D is transferred across the placenta (Ashley et al., 2022) and is important for both fetal and lifelong health, with low pregnancy concentrations linked to low birth weight, obesity and insulin resistance (Harvey et al., 2014; Crozier et al., 2012; Hrudey et al., 2015). Rodent models support the association between *in utero* vitamin D deficiency and poor postnatal cardio-metabolic health in the offspring such as insulin resistance, hypertension and altered fat mass or metabolism (Ideraabdullah et al., 2019). Furthermore, vitamin D induces effects on the placental transcriptome and proteome that are dependent on the underlying epigenetic landscape and in patterns relevant to placental function and therefore its influence on fetal development and subsequent lifelong health (Ashley et al., 2022).

3.3. Placental exposure to toxins during pregnancy

The role of environmental pollutants on the placenta and fetus is of growing interest and relevant exposures include air pollution, endocrine disrupting chemicals and heavy metals. Exposure of the fetoplacental unit is mediated directly via maternal exposures, but the fetus may also be affected indirectly via dysregulation of maternal physiology. Toxins may also derive from products of maternal metabolism that can be harmful if they build up in the mother's circulation. While the placenta acts as barrier for many substances, potentially harmful substances can reach the fetus by crossing the placenta either via diffusion or by utilising existing transport proteins.

3.3.1. Maternal metabolic toxins

An example of maternal disorders which increase exposure of the placenta to toxins is intrahepatic cholestasis of pregnancy where maternal bile acid levels become elevated, which is associated with an increased incidence of fetal death thought to be caused by heart failure (Williamson et al., 2001). Maternal bile acids can cross the placenta via OATP transporters and induce vasoconstriction in placental vessels, potentially reducing its perfusion and placing stress of the developing fetal heart (Lofthouse et al., 2019). In untreated intrahepatic cholestasis of pregnancy, high fetal and maternal serum bile acid concentrations are associated with fetal cardiac dysfunction (Vasavan et al., 2021). Other examples may include genetic disorders such as phenylketonuria where high maternal phenylalanine levels may impair placental amino acid transport (Panitchob et al., 2015).

3.3.2. Air pollution

Air pollution includes that from gases (e.g. nitrous oxides), volatile organic compounds (e.g. Benzene or formaldehyde) and particulate matter (PM, e.g. nanoparticles from diesel combustion). Air pollution is associated with reduced population heath including in early life. While

the mechanisms are unclear, exposure to air pollution during pregnancy, particularly $PM_{2.5}$, is associated with low birth weight and preterm birth, factors which predispose the offspring to increased risk of cardio-metabolic disorders in later life (Stieb et al., 2012). It has been proposed that air pollution affects the placenta by oxidative stress, systemic inflammation, epigenetic changes and ageing mechanisms, which could result in placental insufficiency with decreased transport of nutrients to the developing fetus (van den Hooven et al., 2012; Saenen et al., 2019). Vitamin D deficiency increases the adverse effects of air pollutant exposure ($PM_{2.5}$) during pregnancy with placental DNA methylation mediating this effect (Yang et al., 2020). Changes in placental DNA methylation associated with pollution have been suggested to affect a range of gene pathways that may regulate placental function. These placental epigenetic changes induce abnormal fetal development, resulting in persistent changes in organ function, leading to development of disease (Saenen et al., 2019). The detection of particulates from air pollution within the placenta itself provides a mechanism by which this form of pollution could affect the placenta and potentially be transported to the fetus, inducing direct effects (Liu et al., 2021; Bové et al., 2019). In utero exposure to air pollution in China has been linked to congenital heart defects in the fetus (Zhang et al., 2016), however further studies are warranted in this area.

3.3.3. Endocrine disrupting chemicals

Endocrine disrupting chemicals (EDCs) are exogenous substances that interfere with endogenous hormones and their signalling, disrupting key biological processes. The range of potential EDCs is vast, including bisphenols (BP; e.g. BPA, BPS and BPF), organochlorine pesticides, diethylstilbestrol and phthalates (e.g. di-2-ethylhexylphthalate). Analysis of human tissues reveals exposure is near ubiquitous, with presence in maternal plasma, urine, amniotic fluid and milk. This is of particular concern during sensitive periods of fetal and neonatal life where exposure may disrupt normal development. Transfer of EDCs to the fetus via the placenta is associated with miscarriage, fetal growth retardation and preeclampsia, all of which can associate with postnatal cardiovascular or metabolic health (Tang et al., 2020). BPA exposure occurs primarily through the diet (Rolfo et al., 2020) and can affect placental development, causing abnormal development of trophoblast cells and altered hCG secretion in early trimester trophoblast (Mørck et al., 2010) (Paulesu et al., 2018), as well as having direct effects on the fetus, since the placenta is permeable to BPA (Corbel et al., 2014). EDC exposure may also derive from natural chemicals in foods, such as phytoestrogens that are abundant in soy-based products.

Maternal exposure to EDCs in the first trimester is associated with infant cord blood DNA methylation, suggesting EDCs may have effects across generations via epigenetic mechanisms (Montrose et al., 2018). There is also evidence for effects on the placenta itself, as measured by gene expression and some evidence for epigenetic changes in animal and *in vitro studies* (Strakovsky and Schantz, 2018).

3.3.4. Heavy metals

Heavy metals are present in the environment from a variety of sources, including lead in paint and arsenic in ground water. Heavy metals cross the placenta: heavy metal accumulation in the placenta correlates with maternal and fetal levels, suggesting it may be used as a biomarker for fetal exposure (Punshon et al., 2016). The mechanisms involved, however, are not clear but placental transport of non-essential metals may in part be mediated by the endogenous iron transporter in the basal membrane of the syncytiotrophoblast. Different metals may also affect the placenta differently, for example, one study reported high levels of cadmium in growth restricted fetuses but not in the placentas of these fetuses (Sabra et al., 2017).

Exposure to arsenic is a global problem due to contaminated drinking water, with *in utero* arsenic exposure associated with susceptibility to disease in later in life. In humans, early life arsenic exposure is linked to cardiovascular disease, which is supported by animal models that indicate a role for transplacental arsenic exposure in the development of atherosclerosis (Farzan et al., 2013; Srivastava et al., 2007). Inorganic arsenic is reported to act as an endocrine disruptor in choriocarcinoma cell lines, affecting the glucocorticoid receptor (GR) pathway (Meakin et al., 2020a). Animal models demonstrate epigenetic alterations and changes in gene expression in the offspring following transplacental exposure to arsenic with human placental DNA methylation changes in response to prenatal arsenic exposure supporting a role for epigenetics in transmitting the effects on disease risk (Cardenas et al., 2015).

3.4. Placental exposure to drugs during pregnancy

3.4.1. Pharmaceutical drugs

Exposure to pharmaceuticals during pregnancy is often necessary to protect the mother's health. It is important to note that maintaining maternal health also protects fetal health. Drugs are used to treat maternal asthma (e.g. steroids), metabolic disorders (e.g. statins) and psychological issues (e.g. antidepressants); however, if these drugs affect or cross the placental they may have adverse effects on fetal development.

Maternal use of selective serotonin reuptake inhibitors (SSRIs) to treat depression during pregnancy has been associated with lower birth weight and poor birth outcomes. SSRI use has also been associated with placental histopathological abnormalities, suggesting a mechanism by which they could affect fetal growth and subsequent cardio-metabolic health (Levy et al., 2020). There are also changes in gene and protein expression in placentas from mothers with depression who took SSRIs compared to controls (Edvinsson et al., 2019). Further work to better understand this relationship could help develop safer treatment strategies and reassure mothers about the safety of these drugs.

Placental exposure to corticosteroids can result from maternal stress or pharmacological sources including inhaled steroids to treat asthma or, more acutely, from corticosteroid treatment in women at risk of premature labour. Antenatal corticosteroid treatment for prematurity is highly effective at improving neonatal outcomes but there has long been a concern about longer-term risks for cardio-metabolic health. While follow up studies in children and adults have not identified cardio-metabolic risks, other studies have identified neurophysiological differences (Cartwright et al., 2018). These neurophysiological differences may align with work in rodents showing fetal steroid exposure alters epigenetic regulation of stress responsiveness mechanisms in the brain (Meaney et al., 2007). While the evidence currently indicates that effective asthma treatment in pregnancy does not affect fetal growth (Meakin et al., 2020b), the use of inhaled steroids are associated with altered placental structure and activity of the enzyme 11β-HSD2 which inactivates corticosteroids (Clifton et al., 2006; Mayhew et al., 2008). Epigenetic regulation of key placental genes involved in the response to corticosteroids (11β-HSD2 and glucocorticoid receptor) has been shown to relate to birth weight (Banister et al., 2011; Marsit et al., 2012). Another potential source of fetal corticosteroid exposure is maternal consumption of foods containing 11β-HSD2 inhibitors, such as glycyrrhetinic acid present in liquorice, which reduce the effectiveness of the placental as a barrier to corticosteroids.

3.4.2. Recreational drugs

As with pharmaceutical drugs, recreational drugs may also affect placental function or cross the placenta to affect the fetus directly. Smoking and alcohol are likely to be the most common placental exposures.

Smoking cigarettes during pregnancy is particularly dangerous as both the nicotine and the toxic combustion products can mediate biological effects. Reduced birth weight, infant morbidity and mortality and later disease risk have been associated with exposure to smoking during gestation (Mund et al., 2013). Exposure to maternal smoking can have serious effects on the placenta, influencing placental structure (Jauniaux and Burton, 2007), gene expression (Walker et al., 2019; Day et al.,

2015) and DNA methylation (Markunas et al., 2014), which may impact on fetal development and subsequent postnatal health. Maternal cigarette smoking alters DNA methylation in the placental genome at repetitive elements and in specific genes (Wilhelm-Benartzi et al., 2012) such as cytochrome P450 1A1 (CYP1A1) (Suter et al., 2010). This is potentially a placental protective response to the increased toxin exposure since CYP1A1 detoxifies the harmful compounds in tobacco smoke.

Maternal alcohol consumption has implications for fetal development as alcohol crosses the placenta (Kelly et al., 2000; Floyd et al., 2005). Alcohol can also affect fetal development by reducing placental size, nutrient transport capacity and endocrine function, all factors that can influence the programming of cardio-metabolic disease (Burd et al., 2007). Placental effects may be mediated via epigenetic mechanisms as increased placental global DNA methylation is seen with maternal alcohol intake (Loke et al., 2018).

Maternal use of illegal recreational drugs also affects the placenta, with opiate or cocaine use altering placental vasculature, which may underlie the decreased fetal growth observed with use of these drugs (Ortigosa et al., 2012). Cocaine exposure is associated with silencing of genes important for placental function, suggested to be via DNA hypermethylation in their promoter regions (Salisbury et al., 2009). Delta-9-tetrahydrocannabinol in cannabis can cross the placenta (Hatch and Bracken, 1986) to affect the fetus in terms of growth restriction (Zuckerman et al., 1989), placental abruption, preterm birth, stillbirths and spontaneous miscarriages and therefore the subsequent impacts on postnatal health (Hatch and Bracken, 1986; Felder and Glass, 1998). There may also be direct effects on placental function as the placenta expresses cannabinoid receptors (Helliwell et al., 2004).

4. Placental biomarkers of past exposures and future risks

The term placenta contains biomarkers that can identify its past exposures, referred to as the 'placental phenotype'. If these biomarkers could be clearly linked to patterns of fetal growth or future health outcomes, then these could be an invaluable source of information for predicting future risk of cardio-metabolic disease. Although making predictions of risk of a disease that may not be manifest for 5 or 6 decades is difficult, research to collect and analyse placental biomarkers now will be important to determine any such future relationships.

It has been suggested that placental phenotypes, such as epigenetic markers, structural or biochemical features, could be used to distinguish between fetal growth restriction due to early life environmental exposures *versus* those determined by the baby's genetic propensity to be small (Sibley et al., 2005). It could also allow identification of babies born within the normal birth weight range that did not reach their genetic growth potential. Indeed, placental biomarkers may also help to identify abnormalities that may influence later disease risk, in the absence of any of changes in birthweight, which is only a surrogate, but imperfect, marker of a poor intrauterine environment.

5. Conclusion

The placental exposome has significant potential to influence placenta function and future cardio-metabolic health. There are clear examples of exposures leading to changes in placental epigenetics and structure in ways that may affect placental function and thus fetal development. However, clearly demonstrating the link between placental factors and health outcomes in humans is difficult, both because placental factors are often not measured and because any adverse outcomes may not manifest for many decades. This highlights the importance of population studies, which have collected and banked placental tissue samples for future research purposes. A focus of this research should be to identify how specific exposures affect placental function and which exposures are most likely to have adverse outcomes for the fetus. These studies will inform public health initiatives to reduce exposure to environmental risk factors, providing prospective parents with information on how to optimise health before, during and after pregnancy, for the long-term benefit of their children.

References

Aagaard, Kjersti, Ma, Jun, Antony, Kathleen M., Ganu, Radhika, Petrosino, Joseph, Versalovic, James, 2014. The placenta harbors a unique microbiome. Sci Transl Med. 6 (237), 237–265. https://doi.org/10.1126/scitranslmed.3008599.

Alwasel, S.H., Abotalib, Z., Aljarallah, J.S., Osmond, C., Alkharaz, S.M., Alhazza, I.M., Badr, G., Barker, D.J., 2010. Changes in placental size during Ramadan. Placenta 31 (7), 607–610.

Alwasel, S.H., Harrath, A.H., Aldahmash, W.M., Abotalib, Z., Nyengaard, J.R., Osmond, C., Dilworth, M.R., Al Omar, S.Y., Jerah, A.A., Barker, D.J., 2014. Sex differences in regional specialisation across the placental surface. Placenta 35 (6), 365–369.

Andrews, S.V., Yang, I.J., Froehlich, K., Oskotsky, T., Sirota, M., 2021. Large-scale placenta DNA methylation mega-analysis reveals fetal sex-specific differentially methylated CpG sites and regions. bioRxiv 2021, 03.04.433985.

Ashley, B., Simner, C., Manousopoulou, A., Jenkinson, C., Hey, F., Frost, J.M., Rezwan, F. I., White, C.H., Lofthouse, E.M., Hyde, E., Cooke, L.D.F., Barton, S., Mahon, P., Curtis, E.M., Moon, R.J., Crozier, S.R., Inskip, H.M., Godfrey, K.M., Holloway, J.W., Cooper, C., Jones, K.S., Lewis, R.M., Hewison, M., Garbis, S.D.D., Branco, M.R., Harvey, N.C., Cleal, J.K., 2022 Mar 8. Placental uptake and metabolism of 25(OH) vitamin D determine its activity within the fetoplacental unit. Elife 11, e71094. https://doi.org/10.7554/eLife.71094. PMID: 35256050; PMCID: PMC8903835.

Banister, C.E., Koestler, D.C., Maccani, M.A., Padbury, J.F., Houseman, E.A., Marsit, C.J., 2011. Infant growth restriction is associated with distinct patterns of DNA methylation in human placentas. Epigenetics 6 (7), 920–927.

Barker, D.J., Winter, P.D., Osmond, C., Margetts, B., Simmonds, S.J., 1989. Weight in infancy and death from ischaemic heart disease. Lancet (London, England) 2 (8663), 577–580.

Bové, H., Bongaerts, E., Slenders, E., Bijnens, E.M., Saenen, N.D., Gyselaers, W., Van Eyken, P., Plusquin, M., Roeffaers, M.B.J., Ameloot, M., Nawrot, T.S., 2019. Ambient black carbon particles reach the fetal side of human placenta. Nat. Commun. 10 (1), 3866.

Burd, L., Roberts, D., Olson, M., Odendaal, H., 2007. Ethanol and the placenta: a review, the journal of maternal-fetal & neonatal medicine : the official journal of the European association of perinatal medicine, the federation of asia and oceania perinatal societies. Int.Soc. Perinatal Obstet 20 (5), 361–375.

Burton, G.J., Fowden, A.L., Thornburg, K.L., 2016. Placental origins of chronic disease. Physiol. Rev. 96 (4), 1509–1565.

Butel, M.J., Waligora-Dupriet, A.J., Wydau-Dematteis, S., 2018. The developing gut microbiota and its consequences for health. J. Dev.Orig.Health Dis. 9 (6), 590–597.

Caetano, L., Eckert, J.J., Johnston, D., Chatelet, D.S., Tumbarello, D.A., Smyth, N.R., Ingamells, S., Price, A., Fleming, T.P., 2021. Blastocyst trophectoderm endocytic activation, a marker of adverse developmental programming. Reproduction (Cambridge, England) 162 (4), 289–306.

Cardenas, A., Houseman, E.A., Baccarelli, A.A., Quamruzzaman, Q., Rahman, M., Mostofa, G., Wright, R.O., Christiani, D.C., Kile, M.L., 2015. In utero arsenic exposure and epigenome-wide associations in placenta, umbilical artery, and human umbilical vein endothelial cells. Epigenetics 10 (11), 1054–1063.

Cartwright, R.D., Harding, J.E., Crowther, C.A., Cutfield, W.S., Battin, M.R., Dalziel, S.R., McKinlay, C.J.D., 2018. Repeat antenatal betamethasone and cardiometabolic outcomes. Pediatrics 142 (1).

Cetin, I., 2003. Placental transport of amino acids in normal and growth-restricted pregnancies. Eur. J. Obstet. Gynecol. Reprod. Biol. 110 (Suppl. 1), S50–S54.

Chen, S.L., Shi, X.Y., Zheng, H.Y., Wu, F.R., Luo, C., 2010. Aberrant DNA methylation of imprinted H19 gene in human preimplantation embryos. Fertil. Steril. 94 (6), 2356–2358, 2358.e1.

Christoforou, E.R., Sferruzzi-Perri, A.N., 2020. Molecular mechanisms governing offspring metabolic programming in rodent models of in utero stress. Cell. Mol. Life Sci. : CMLS 77 (23), 4861–4898.

Clare, C.E., Pestinger, V., Kwong, W.Y., Tutt, D.A.R., Xu, J., Byrne, H.M., Barrett, D.A., Emes, R.D., Sinclair, K.D., 2021. Interspecific variation in one-carbon metabolism within the ovarian follicle, oocyte, and preimplantation embryo: consequences for epigenetic programming of DNA methylation. Int. J. Mol. Sci. 22 (4).

Clifton, V.L., Rennie, N., Murphy, V.E., 2006. Effect of inhaled glucocorticoid treatment on placental 11beta-hydroxysteroid dehydrogenase type 2 activity and neonatal birthweight in pregnancies complicated by asthma. Aust. N. Z. J. Obstet. Gynaecol. 46 (2), 136–140.

Cohen, J.A., Rychik, J., Savla, J.J., 2021. The placenta as the window to congenital heart disease. Curr. Opin. Cardiol. 36 (1), 56–60.

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

Constância, M., Hemberger, M., Hughes, J., Dean, W., Ferguson-Smith, A., Fundele, R., Stewart, F., Kelsey, G., Fowden, A., Sibley, C., Reik, W., 2002. Placental-specific IGF-II is a major modulator of placental and fetal growth. Nature 417 (6892), 945–948.

Corbel, T., Gayrard, V., Puel, S., Lacroix, M.Z., Berrebi, A., Gil, S., Viguié, C., Toutain, P. L., Picard-Hagen, N., 2014. Bidirectional placental transfer of Bisphenol A and its main metabolite, Bisphenol A-Glucuronide, in the isolated perfused human placenta. Reproductive toxicology (Elmsford, N.Y.) 47, 51–58.

Cropley, J.E., Eaton, S.A., Aiken, A., Young, P.E., Giannoulatou, E., Ho, J.W.K., Buckland, M.E., Keam, S.P., Hutvagner, G., Humphreys, D.T., Langley, K.G., Henstridge, D.C., Martin, D.I.K., Febbraio, M.A., Suter, C.M., 2016. Male-lineage

transmission of an acquired metabolic phenotype induced by grand-paternal obesity. Mol. Metabol. 5 (8), 699–708.
Crozier, S.R., Harvey, N.C., Inskip, H.M., Godfrey, K.M., Cooper, C., Robinson, S.M., 2012. Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. Am. J. Clin. Nutr. 96 (1), 57–63.
Day, P.E., Cleal, J.K., Lofthouse, E.M., Hanson, M.A., Lewis, R.M., 2013. What factors determine placental glucose transfer kinetics? Placenta 34 (10), 953–958.
Day, P.E., Ntani, G., Crozier, S.R., Mahon, P.A., Inskip, H.M., Cooper, C., Harvey, N.C., Godfrey, K.M., Hanson, M.A., Lewis, R.M., Cleal, J.K., 2015. Maternal factors are associated with the expression of placental genes involved in amino acid metabolism and transport. PLoS One 10 (12), e0143653.
Diaz, P., Powell, T.L., Jansson, T., 2014. The role of placental nutrient sensing in maternal-fetal resource allocation. Biol. Reprod. 91 (4), 82.
Diouf, I., Botton, J., Charles, M.A., Morel, O., Forhan, A., Kaminski, M., Heude, B., 2014. Specific role of maternal weight change in the first trimester of pregnancy on birth size. Matern. Child Nutr. 10 (3), 315–326.
Dwi Putra, S.E., Reichetzeder, C., Hasan, A.A., Slowinski, T., Chu, C., Krämer, B.K., Kleuser, B., Hocher, B., 2020. Being born large for gestational age is associated with increased global placental DNA methylation. Sci. Rep. 10 (1), 927.
Eckert, J.J., Porter, R., Watkins, A.J., Burt, E., Brooks, S., Leese, H.J., Humpherson, P.G., Cameron, I.T., Fleming, T.P., 2012. Metabolic induction and early responses of mouse blastocyst developmental programming following maternal low protein diet affecting life-long health. PLoS One 7 (12), e52791.
Edvinsson, Å., Hellgren, C., Kunovac Kallak, T., Åkerud, H., Skalkidou, A., Stener-Victorin, E., Fornes, R., Spigset, O., Lager, S., Olivier, J., Sundström-Poromaa, I., 2019. The effect of antenatal depression and antidepressant treatment on placental tissue: a protein-validated gene expression study. BMC Pregnancy Childbirth 19 (1), 479.
Eriksson, J.G., Kajantie, E., Osmond, C., Thornburg, K., Barker, D.J., 2010. Boys live dangerously in the womb. Am. J. Hum. Biol. 22 (3), 330–335.
Escobar, J., Gormaz, M., Arduini, A., Gosens, K., Martinez, A., Perales, A., Escrig, R., Tormos, E., Roselló, M., Orellana, C., Vento, M., 2012. Expression of aquaporins early in human pregnancy. Early Hum. Dev. 88 (8), 589–594.
Falkner, B., 2020. Maternal and gestational influences on childhood blood pressure. Pediatr. Nephrol. 35 (8), 1409–1418.
Farzan, S.F., Karagas, M.R., Chen, Y., 2013. In utero and early life arsenic exposure in relation to long-term health and disease. Toxicol. Appl. Pharmacol. 272 (2), 384–390.
Feig, D.S., Donovan, L.E., Corcoy, R., Murphy, K.E., Amiel, S.A., Hunt, K.F., Asztalos, E., Barrett, J.F.R., Sanchez, J.J., de Leiva, A., Hod, M., Jovanovic, L., Keely, E., McManus, R., Hutton, E.K., Meek, C.L., Stewart, Z.A., Wysocki, T., O'Brien, R., Ruedy, K., Kollman, C., Tomlinson, G., Murphy, H.R., 2017. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet (London, England) 390 (10110), 2347–2359.
Felder, C.C., Glass, M., 1998. Cannabinoid receptors and their endogenous agonists. Annu. Rev. Pharmacol. Toxicol. 38, 179–200.
Filiberto, A.C., Maccani, M.A., Koestler, D., Wilhelm-Benartzi, C., Avissar-Whiting, M., Banister, C.E., Gagne, L.A., Marsit, C.J., 2011. Birthweight is associated with DNA promoter methylation of the glucocorticoid receptor in human placenta. Epigenetics 6 (5), 566–572.
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., Godfrey, K.M., 2018. Origins of lifetime health around the time of conception: causes and consequences. Lancet (London, England) 391 (10132), 1842–1852.
Floyd, R.L., O'Connor, M.J., Sokol, R.J., Bertrand, J., Cordero, J.F., 2005. Recognition and prevention of fetal alcohol syndrome. Obstet. Gynecol. 106 (5 Pt 1), 1059–1064.
Gallo, L.A., Barrett, H.L., Dekker Nitert, M., 2017. Review: placental transport and metabolism of energy substrates in maternal obesity and diabetes. Placenta 54, 59–67.
Gama-Sosa, M.A., Wang, R.Y., Kuo, K.C., Gehrke, C.W., Ehrlich, M., 1983. The 5-methylcytosine content of highly repeated sequences in human DNA. Nucleic Acids Res. 11 (10), 3087–3095.
Gao, H., Yallampalli, U., Yallampalli, C., 2012. Maternal protein restriction reduces expression of angiotensin I-converting enzyme 2 in rat placental labyrinth zone in late pregnancy. Biol. Reprod. 86 (2), 31.
Gong, L., Pan, Y.X., Chen, H., 2010. Gestational low protein diet in the rat mediates Igf2 gene expression in male offspring via altered hepatic DNA methylation. Epigenetics 5 (7), 619–626.
Halloran, K.M., Hoskins, E.C., Stenhouse, C., Moses, R.M., Dunlap, K.A., Satterfield, M.C., Seo, H., Johnson, G.A., Wu, G., Bazer, F.W., 2021. Pre-implantation exogenous progesterone and pregnancy in sheep. II. Effects on fetal-placental development and nutrient transporters in late pregnancy. J. Anim. Sci. Biotechnol. 12 (1), 46.
Hanson, M.A., Gluckman, P.D., 2014. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol. Rev. 94 (4), 1027–1076.
Harvey, N.C., Holroyd, C., Ntani, G., Javaid, K., Cooper, P., Moon, R., Cole, Z., Tinati, T., Godfrey, K., Dennison, E., Bishop, N.J., Baird, J., Cooper, C., 2014. Vitamin D supplementation in pregnancy: a systematic review. Health Technol. Assess. 18 (45), 1–190.
Hatch, E.E., Bracken, M.B., 1986. Effect of marijuana use in pregnancy on fetal growth. Am. J. Epidemiol. 124 (6), 986–993.
Heijmans, B.T., Tobi, E.W., Stein, A.D., Putter, H., Blauw, G.J., Susser, E.S., Slagboom, P. E., Lumey, L.H., 2008. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc. Natl. Acad. Sci. U. S. A 105 (44), 17046–17049.
Helliwell, R.J., Chamley, L.W., Blake-Palmer, K., Mitchell, M.D., Wu, J., Kearn, C.S., Glass, M., 2004. Characterization of the endocannabinoid system in early human pregnancy. J.Clin. Endocrinol. Metabol. 89 (10), 5168–5174.
Hemachandra, A.H., Klebanoff, M.A., Duggan, A.K., Hardy, J.B., Furth, S.L., 2006. The association between intrauterine growth restriction in the full-term infant and high blood pressure at age 7 years: results from the Collaborative Perinatal Project. Int. J. Epidemiol. 35 (4), 871–877.
Hirschmugl, B., Desoye, G., Catalano, P., Klymiuk, I., Scharnagl, H., Payr, S., Kitzinger, E., Schliefsteiner, C., Lang, U., Wadsack, C., Hauguel-de Mouzon, S., 2017. Maternal obesity modulates intracellular lipid turnover in the human term placenta. Int. J. Obes. 41 (2), 317–323 (2005).
Hoyo, C., Fortner, K., Murtha, A.P., Schildkraut, J.M., Soubry, A., Demark-Wahnefried, W., Jirtle, R.L., Kurtzberg, J., Forman, M.R., Overcash, F., Huang, Z., Murphy, S.K., 2012. Association of cord blood methylation fractions at imprinted insulin-like growth factor 2 (IGF2), plasma IGF2, and birth weight. Cancer Causes Control 23 (4), 635–645.
Hrudey, E.J., Reynolds, R.M., Oostvogels, A.J., Brouwer, I.A., Vrijkotte, T.G., 2015. The association between maternal 25-hydroxyvitamin D concentration during gestation and early childhood cardio-metabolic outcomes: is there interaction with pre-pregnancy BMI? PLoS One 10 (8), e0133313.
Ideraabdullah, F.Y., Belenchia, A.M., Rosenfeld, C.S., Kullman, S.W., Knuth, M., Mahapatra, D., Bereman, M., Levin, E.D., Peterson, C.A., 2019. Maternal vitamin D deficiency and developmental origins of health and disease (DOHaD). J. Endocrinol.
Ito, M., Itakura, A., Ohno, Y., Nomura, M., Senga, T., Nagasaka, T., Mizutani, S., 2002. Possible activation of the renin-angiotensin system in the feto-placental unit in preeclampsia. J.Clin. Endocrinol. Metabol. 87 (4), 1871–1878.
Jansson, T., Powell, T.L., 2013. Role of placental nutrient sensing in developmental programming. Clin. Obstet. Gynecol. 56 (3), 591–601.
Jansson, T., Ylven, K., Wennergren, M., Powell, T.L., 2002. Glucose transport and system A activity in syncytiotrophoblast microvillous and basal plasma membranes in intrauterine growth restriction. Placenta 23 (5), 392–399.
Jansson, N., Pettersson, J., Haafiz, A., Ericsson, A., Palmberg, I., Tranberg, M., Ganapathy, V., Powell, T.L., Jansson, T., 2006a. Down-regulation of placental transport of amino acids precedes the development of intrauterine growth restriction in rats fed a low protein diet. J. Physiol. 576 (Pt 3), 935–946.
Jansson, T., Cetin, I., Powell, T.L., Desoye, G., Radaelli, T., Ericsson, A., Sibley, C.P., 2006b. Placental transport and metabolism in fetal overgrowth – a workshop report. Placenta 27 (Suppl. A), S109–S113.
Januar, V., Desoye, G., Novakovic, B., Cvitic, S., Saffery, R., 2015. Epigenetic regulation of human placental function and pregnancy outcome: considerations for causal inference. Am. J. Obstet. Gynecol. 213 (4 Suppl. l), S182–S196.
Jauniaux, E., Burton, G.J., 2007. Morphological and biological effects of maternal exposure to tobacco smoke on the feto-placental unit. Early Hum. Dev. 83 (11), 699–706.
Kallas-Koeman, M.M., Kong, J.M., Klinke, J.A., Butalia, S., Lodha, A.K., Lim, K.I., Duan, Q.M., Donovan, L.E., 2014. Insulin pump use in pregnancy is associated with lower HbA1c without increasing the rate of severe hypoglycaemia or diabetic ketoacidosis in women with type 1 diabetes. Diabetologia 57 (4), 681–689.
Kapourchali, F.R., Cresci, G.A.M., 2020. Early-life gut microbiome-the importance of maternal and infant factors in its establishment, nutrition in clinical practice. Off. Publ. Am.Soc.Parenter. Enteral Nutr. 35 (3), 386–405.
Kelly, S.J., Day, N., Streissguth, A.P., 2000. Effects of prenatal alcohol exposure on social behavior in humans and other species. Neurotoxicol. Teratol. 22 (2), 143–149.
Khajah, M.A., Fateel, M.M., Ananthalakshmi, K.V., Luqmani, Y.A., 2016. Anti-inflammatory action of angiotensin 1-7 in experimental colitis. PLoS One 11 (3), e0150861.
Lazaraviciute, G., Kauser, M., Bhattacharya, S., Haggarty, P., Bhattacharya, S., 2014. A systematic review and meta-analysis of DNA methylation levels and imprinting disorders in children conceived by IVF/ICSI compared with children conceived spontaneously. Hum. Reprod. Update 20 (6), 840–852.
Leary, C., Leese, H.J., Sturmey, R.G., 2015. Human embryos from overweight and obese women display phenotypic and metabolic abnormalities. Human reproduction (Oxford, England) 30 (1), 122–132.
Levy, M., Kovo, M., Miremberg, H., Anchel, N., Herman, H.G., Bar, J., Schreiber, L., Weiner, E., 2020. Maternal use of selective serotonin reuptake inhibitors (SSRI) during pregnancy-neonatal outcomes in correlation with placental histopathology. J. Perinatol. : Off. J. Calif.Perinatal.Assoc. 40 (7), 1017–1024.
Lewis, R.M., Petry, C.J., Ozanne, S.E., Hales, C.N., 2001. Effects of maternal iron restriction in the rat on blood pressure, glucose tolerance, and serum lipids in the 3-month-old offspring. Metabolism 50 (5), 562–567.
Lewis, R.M., Greenwood, S.L., Cleal, J.K., Crozier, S.R., Verrall, L., Inskip, H.M., Cameron, I.T., Cooper, C., Sibley, C.P., Hanson, M.A., Godfrey, K.M., 2010. Maternal muscle mass may influence system A activity in human placenta. Placenta 31 (5), 418–422.
Lewis, R.M., Cleal, J.K., Hanson, M.A., 2012. Review: placenta, evolution and lifelong health. Placenta 33 (Suppl. l), S28–S32.
Lewis, R.M., Demmelmair, H., Gaillard, R., Godfrey, K.M., Hauguel-de, M.S., Huppertz, B., Larque, E., Saffery, R., Symonds, M.E., Desoye, G., 2013. The placental exposome: placental determinants of fetal adiposity and postnatal body composition. Ann. Nutr. Metab. 63 (3), 208–215.
Linask, K.K., Han, M., Bravo-Valenzuela, N.J., 2014. Changes in vitelline and utero-placental hemodynamics: implications for cardiovascular development. Front. Physiol. 5, 390.
Liu, N.M., Miyashita, L., Maher, B.A., McPhail, G., Jones, C.J.P., Barratt, B., Thangaratinam, S., Karloukovski, V., Ahmed, I.A., Aslam, Z., Grigg, J., 2021.

Evidence for the presence of air pollution nanoparticles in placental tissue cells. Sci. Total Environ. 751, 142235.
Lofthouse, E.M., Torrens, C., Manousopoulou, A., Nahar, M., Cleal, J.K., O'Kelly, I.M., Sengers, B.G., Garbis, S.D., Lewis, R.M., 2019. Ursodeoxycholic acid inhibits uptake and vasoconstrictor effects of taurocholate in human placenta. Faseb. J. : Off. Publ. Fed. Am. Soc.Exp. Biol. 33 (7), 8211–8220.
Loke, Y.J., Muggli, E., Nguyen, L., Ryan, J., Saffery, R., Elliott, E.J., Halliday, J., Craig, J. M., 2018. Time- and sex-dependent associations between prenatal alcohol exposure and placental global DNA methylation. Epigenomics 10 (7), 981–991.
Maffeis, C., Morandi, A., 2017. Effect of maternal obesity on foetal growth and metabolic health of the offspring. Obesity facts 10 (2), 112–117.
Markunas, C.A., Xu, Z., Harlid, S., Wade, P.A., Lie, R.T., Taylor, J.A., Wilcox, A.J., 2014. Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. Environ. Health Perspect. 122 (10), 1147–1153.
Marsit, C.J., Maccani, M.A., Padbury, J.F., Lester, B.M., 2012. Placental 11-beta hydroxysteroid dehydrogenase methylation is associated with newborn growth and a measure of neurobehavioral outcome. PLoS One 7 (3), e33794.
Matthiesen, N.B., Henriksen, T.B., Agergaard, P., Gaynor, J.W., Bach, C.C., Hjortdal, V.E., Østergaard, J.R., 2016. Congenital heart defects and indices of placental and fetal growth in a nationwide study of 924 422 liveborn infants. Circulation 134 (20), 1546–1556.
Mayhew, T.M., Charnock-Jones, D.S., Kaufmann, P., 2004. Aspects of human fetoplacental vasculogenesis and angiogenesis. III. Changes in complicated pregnancies. Placenta 25 (2–3), 127–139.
Mayhew, T.M., Jenkins, H., Todd, B., Clifton, V.L., 2008. Maternal asthma and placental morphometry: effects of severity, treatment and fetal sex. Placenta 29 (4), 366–373.
Meakin, C.J., Szilagyi, J.T., Avula, V., Fry, R.C., 2020a. Inorganic arsenic and its methylated metabolites as endocrine disruptors in the placenta: mechanisms underpinning glucocorticoid receptor (GR) pathway perturbations. Toxicol. Appl. Pharmacol. 409, 115305.
Meakin, A.S., Saif, Z., Seedat, N., Clifton, V.L., 2020b. The impact of maternal asthma during pregnancy on fetal growth and development: a review. Expet Rev. Respir. Med. 14 (12), 1207–1216.
Meaney, M.J., Szyf, M., Seckl, J.R., 2007. Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. Trends Mol. Med. 13 (7), 269–277.
Montrose, L., Padmanabhan, V., Goodrich, J.M., Domino, S.E., Treadwell, M.C., Meeker, J.D., Watkins, D.J., Dolinoy, D.C., 2018. Maternal levels of endocrine disrupting chemicals in the first trimester of pregnancy are associated with infant cord blood DNA methylation. Epigenetics 13 (3), 301–309.
Mørck, T.J., Sorda, G., Bechi, N., Rasmussen, B.S., Nielsen, J.B., Ietta, F., Rytting, E., Mathiesen, L., Paulesu, L., Knudsen, L.E., 2010. Placental transport and in vitro effects of Bisphenol A. Reproductive toxicology (Elmsford, N.Y.) 30 (1), 131–137.
Mueller, N.T., Shin, H., Pizoni, A., Werlang, I.C., Matte, U., Goldani, M.Z., Goldani, H.A., Dominguez-Bello, M.G., 2016. Birth mode-dependent association between pre-pregnancy maternal weight status and the neonatal intestinal microbiome. Sci. Rep. 6, 23133.
Mund, M., Louwen, F., Klingelhoefer, D., Gerber, A., 2013. Smoking and pregnancy–a review on the first major environmental risk factor of the unborn. Int. J. Environ. Res. Publ. Health 10 (12), 6485–6499.
Novakovic, B., Saffery, R., 2012. The ever growing complexity of placental epigenetics - role in adverse pregnancy outcomes and fetal programming. Placenta 33 (12), 959–970.
Novakovic, B., Gordon, L., Robinson, W.P., Desoye, G., Saffery, R., 2013. Glucose as a fetal nutrient: dynamic regulation of several glucose transporter genes by DNA methylation in the human placenta across gestation. J. Nutr. Biochem. 24 (1), 282–288.
Oberlander, T.F., Weinberg, J., Papsdorf, M., Grunau, R., Misri, S., Devlin, A.M., 2008. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses. Epigenetics 3 (2), 97–106.
Olomu, I.N., Pena-Cortes, L.C., Long, R.A., Vyas, A., Krichevskiy, O., Luellwitz, R., Singh, P., Mulks, M.H., 2020. Elimination of "kitome" and "splashome" contamination results in lack of detection of a unique placental microbiome. BMC Microbiol. 20 (1), 157.
Ortigosa, S., Friguls, B., Joya, X., Martinez, S., Marinoso, M.L., Alameda, F., Vall, O., Garcia-Algar, O., 2012. Feto-placental morphological effects of prenatal exposure to drugs of abuse. Reprod. Toxicol. 34 (1), 73–79.
Panitchob, N., Widdows, K.L., Crocker, I.P., Hanson, M.A., Johnstone, E.D., Please, C.P., Sibley, C.P., Glazier, J.D., Lewis, R.M., Sengers, B.G., 2015. Computational modelling of amino acid exchange and facilitated transport in placental membrane vesicles. J. Theor. Biol. 365, 352–364.
Paulesu, L., Rao, C.V., Ietta, F., Pietropolli, A., Ticconi, C., 2018. hCG and its disruption by environmental contaminants during human pregnancy. Int. J. Mol. Sci. 19 (3).
Perez-Garcia, V., Fineberg, E., Wilson, R., Murray, A., Mazzeo, C.I., Tudor, C., Sienerth, A., White, J.K., Tuck, E., Ryder, E.J., Gleeson, D., Siragher, E., Wardle-Jones, H., Staudt, N., Wali, N., Collins, J., Geyer, S., Busch-Nentwich, E.M., Galli, A., Smith, J.C., Robertson, E., Adams, D.J., Weninger, W.J., Mohun, T., Hemberger, M., 2018. Placentation defects are highly prevalent in embryonic lethal mouse mutants. Nature 555 (7697), 463–468.
Pérez-Pérez, A., Vilariño-García, T., Dietrich, V., Guadix, P., Dueñas, J.L., Varone, C.L., Damiano, A.E., Sánchez-Margalet, V., 2020. Aquaporins and placenta, Vitamins and hormones 112, 311–326.
Pringle, K.G., Tadros, M.A., Callister, R.J., Lumbers, E.R., 2011. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? Placenta 32 (12), 956–962.
Punshon, T., Li, Z., Marsit, C.J., Jackson, B.P., Baker, E.R., Karagas, M.R., 2016. Placental metal concentrations in relation to maternal and infant toenails in a U.S. Cohort. Environ. Sci. Technol. 50 (3), 1587–1594.
Rahnama, F., Shafiei, F., Gluckman, P.D., Mitchell, M.D., Lobie, P.E., 2006. Epigenetic regulation of human trophoblastic cell migration and invasion. Endocrinology 147 (11), 5275–5283.
Reamon-Buettner, S.M., Buschmann, J., Lewin, G., 2014. Identifying placental epigenetic alterations in an intrauterine growth restriction (IUGR) rat model induced by gestational protein deficiency. Reprod. Toxicol. 45, 117–124.
Reik, W., Dean, W., Walter, J., 2001. Epigenetic reprogramming in mammalian development. Science (New York, N.Y.) 293 (5532), 1089–1093.
Risnes, K.R., Romundstad, P.R., Nilsen, T.I., Eskild, A., Vatten, L.J., 2009. Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women. Am. J. Epidemiol. 170 (5), 622–631.
Rivera, R.M., 2019. Consequences of assisted reproductive techniques on the embryonic epigenome in cattle. Reprod. Fertil. Dev. 32 (2), 65–81.
Rivera, R.M., Stein, P., Weaver, J.R., Mager, J., Schultz, R.M., Bartolomei, M.S., 2008. Manipulations of mouse embryos prior to implantation result in aberrant expression of imprinted genes on day 9.5 of development. Hum. Mol. Genet. 17 (1), 1–14.
Rolfo, A., Nuzzo, A.M., De Amicis, R., Moretti, L., Bertoli, S., Leone, A., 2020. Fetal-maternal exposure to endocrine disruptors: correlation with diet intake and pregnancy outcomes. Nutrients 12 (6).
Roos, S., Palmberg, I., Saljo, K., Powell, T.L., Jansson, T., 2005. Expression of placental mammalian target of rapamycin (mTOR) is altered in relation to fetal growth and mTOR regulates leucine transport. Placenta 26 (8–9). A9-A9.
Roos, S., Kanai, Y., Prasad, P.D., Powell, T.L., Jansson, T., 2009. Regulation of placental amino acid transporter activity by mammalian target of rapamycin. Am. J. Physiol. Cell Physiol. 296 (1), C142–C150.
Sabra, S., Malmqvist, E., Saborit, A., Gratacós, E., Gomez Roig, M.D., 2017. Heavy metals exposure levels and their correlation with different clinical forms of fetal growth restriction. PLoS One 12 (10), e0185645.
Saenen, N.D., Martens, D.S., Neven, K.Y., Alfano, R., Bové, H., Janssen, B.G., Roels, H.A., Plusquin, M., Vrijens, K., Nawrot, T.S., 2019. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? Clin. Epigenet. 11 (1), 124.
Saif, Z., Hodyl, N.A., Hobbs, E., Tuck, A.R., Butler, M.S., Osei-Kumah, A., Clifton, V.L., 2014. The human placenta expresses multiple glucocorticoid receptor isoforms that are altered by fetal sex, growth restriction and maternal asthma. Placenta 35 (4), 260–268.
Salisbury, A.L., Ponder, K.L., Padbury, J.F., Lester, B.M., 2009. Fetal effects of psychoactive drugs. Clin. Perinatol. 36 (3), 595–619.
Santos, R.A., Simoes e Silva, A.C., Maric, C., Silva, D.M., Machado, R.P., de Buhr, I., Heringer-Walther, S., Pinheiro, S.V., Lopes, M.T., Bader, M., Mendes, E.P., Lemos, V. S., Campagnole-Santos, M.J., Schultheiss, H.P., Speth, R., Walther, T., 2003. Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. Proc. Natl. Acad. Sci. U.S.A. 100 (14), 8258–8263.
Satokari, R., Grönroos, T., Laitinen, K., Salminen, S., Isolauri, E., 2009. Bifidobacterium and Lactobacillus DNA in the human placenta. Lett. Appl. Microbiol. 48 (1), 8–12.
Segura, M.T., Demmelmair, H., Krauss-Etschmann, S., Nathan, P., Dehmel, S., Padilla, M. C., Rueda, R., Koletzko, B., Campoy, C., 2017. Maternal BMI and gestational diabetes alter placental lipid transporters and fatty acid composition. Placenta 57, 144–151.
Sferruzzi-Perri, A.N., Camm, E.J., 2016. The programming power of the placenta. Front. Physiol. 7, 33.
Sibley, C.P., Turner, M.A., Cetin, I., Ayuk, P., Boyd, C.A., D'Souza, S.W., Glazier, J.D., Greenwood, S.L., Jansson, T., Powell, T., 2005. Placental phenotypes of intrauterine growth. Pediatr. Res. 58 (5), 827–832.
Simner, C., Novakovic, B., Lillycrop, K.A., Bell, C.G., Harvey, N.C., Cooper, C., Saffery, R., Lewis, R.M., Cleal, J.K., 2017. DNA methylation of amino acid transporter genes in the human placenta. Placenta 60, 64–73.
Simões e Silva, A.C., Silveira, K.D., Ferreira, A.J., Teixeira, M.M., 2013. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. Br. J. Pharmacol. 169 (3), 477–492.
Srivastava, S., D'Souza, S.E., Sen, U., States, J.C., 2007. In utero arsenic exposure induces early onset of atherosclerosis in ApoE-/- mice. Reprod. Toxicol. 23 (3), 449–456.
St-Pierre, J., Hivert, M.F., Perron, P., Poirier, P., Guay, S.P., Brisson, D., Bouchard, L., 2012. IGF2 DNA methylation is a modulator of newborn's fetal growth and development. Epigenetics 7 (10), 1125–1132.
Stanirowski, P.J., Szukiewicz, D., Pazura-Turowska, M., Sawicki, W., Cendrowski, K., 2018. Placental expression of glucose transporter proteins in pregnancies complicated by gestational and pregestational diabetes mellitus. Can. J. Diabetes 42 (2), 209–217.
Stark, M.J., Wright, I.M., Clifton, V.L., 2009. Sex-specific alterations in placental 11beta-hydroxysteroid dehydrogenase 2 activity and early postnatal clinical course following antenatal betamethasone. Am. J. Physiol. Regul. Integr. Comp. Physiol. 297 (2), R510–R514.
Stephenson, J., Heslehurst, N., Hall, J., Schoenaker, D., Hutchinson, J., Cade, J.E., Poston, L., Barrett, G., Crozier, S.R., Barker, M., Kumaran, K., Yajnik, C.S., Baird, J., Mishra, G.D., 2018. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. Lancet (London, England) 391 (10132), 1830–1841.
Stieb, D.M., Chen, L., Eshoul, M., Judek, S., 2012. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ. Res. 117, 100–111.

Strakovsky, R.S., Schantz, S.L., 2018. Impacts of bisphenol A (BPA) and phthalate exposures on epigenetic outcomes in the human placenta. Environmental epigenetics 4 (3), dvy022.
Sunde, A., Brison, D., Dumoulin, J., Harper, J., Lundin, K., Magli, M.C., Van den Abbeel, E., Veiga, A., 2016. Time to take human embryo culture seriously. Human reproduction (Oxford, England) 31 (10), 2174–2182.
Suter, M., Abramovici, A., Showalter, L., Hu, M., Shope, C.D., Varner, M., Aagaard-Tillery, K., 2010. In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. Metabolism 59 (10), 1481–1490.
Swanson, L.D., Bewtra, C., 2008. Increase in normal placental weights related to increase in maternal body mass index, the journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies. Int.Soc. Perinatal Obstet 21 (2), 111–113.
Tallant, E.A., Ferrario, C.M., Gallagher, P.E., 2005. Angiotensin-(1-7) inhibits growth of cardiac myocytes through activation of the mas receptor. Am. J. Physiol. Heart Circ. Physiol. 289 (4), H1560–H1566.
Tamanna, S., Clifton, V.L., Rae, K., van Helden, D.F., Lumbers, E.R., Pringle, K.G., 2020. Angiotensin converting enzyme 2 (ACE2) in pregnancy: preeclampsia and small for gestational age. Front. Physiol. 11, 590787.
Tamanna, S., Lumbers, E.R., Morosin, S.K., Delforce, S.J., Pringle, K.G., 2021. ACE2: a key modulator of the renin-angiotensin system and pregnancy. Am. J. Physiol. Regul. Integr. Comp. Physiol. 321 (6), R833–r843.
Tang, Z.R., Xu, X.L., Deng, S.L., Lian, Z.X., Yu, K., 2020. Oestrogenic endocrine disruptors in the placenta and the fetus. Int. J. Mol. Sci. 21 (4).
Tomat, A.L., Costa Mde, L., Arranz, C.T., 2011. Zinc restriction during different periods of life: influence in renal and cardiovascular diseases. Nutrition 27 (4), 392–398.
Tun, H.M., Bridgman, S.L., Chari, R., Field, C.J., Guttman, D.S., Becker, A.B., Mandhane, P.J., Turvey, S.E., Subbarao, P., Sears, M.R., Scott, J.A., Kozyrskyj, A.L., 2018. Roles of birth mode and infant gut microbiota in intergenerational transmission of overweight and obesity from mother to offspring. JAMA Pediatr. 172 (4), 368–377.
Turan, N., Katari, S., Gerson, L.F., Chalian, R., Foster, M.W., Gaughan, J.P., Coutifaris, C., Sapienza, C., 2010. Inter- and intra-individual variation in allele-specific DNA methylation and gene expression in children conceived using assisted reproductive technology. PLoS Genet. 6 (7), e1001033.
Turco, M.Y., Moffett, A., 2019. Development of the human placenta. Development (Cambridge, England) 146 (22).
Valdés, G., Corthorn, J., Bharadwaj, M.S., Joyner, J., Schneider, D., Brosnihan, K.B., 2013. Utero-placental expression of angiotensin-(1-7) and ACE2 in the pregnant Guinea-pig. Reprod. Biol. Endocrinol. : RBE (Rev. Bras. Entomol.) 11, 5.
van Abeelen, A.F., de Rooij, S.R., Osmond, C., Painter, R.C., Veenendaal, M.V., Bossuyt, P.M., Elias, S.G., Grobbee, D.E., van der Schouw, Y.T., Barker, D.J., Roseboom, T.J., 2011. The sex-specific effects of famine on the association between placental size and later hypertension. Placenta 32 (9), 694–698.
van den Hooven, E.H., Pierik, F.H., de Kluizenaar, Y., Hofman, A., van Ratingen, S.W., Zandveld, P.Y., Russcher, H., Lindemans, J., Miedema, H.M., Steegers, E.A., Jaddoe, V.W., 2012. Air pollution exposure and markers of placental growth and function: the generation R study. Environ. Health Perspect. 120 (12), 1753–1759.
Vasavan, T., Deepak, S., Jayawardane, I.A., Lucchini, M., Martin, C., Geenes, V., Yang, J., Lövgren-Sandblom, A., Seed, P.T., Chambers, J., Stone, S., Kurlak, L., Dixon, P.H., Marschall, H.U., Gorelik, J., Chappell, L., Loughna, P., Thornton, J., Pipkin, F.B., Hayes-Gill, B., Fifer, W.P., Williamson, C., 2021. Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. J. Hepatol. 74 (5), 1087–1096.
Vaughan, O.R., Rosario, F.J., Powell, T.L., Jansson, T., 2017. Regulation of placental amino acid transport and fetal growth. Prog. Mol. Biol.Transl. Sci. 145, 217–251.
Vickers, M.H., Clayton, Z.E., Yap, C., Sloboda, D.M., 2011. Maternal fructose intake during pregnancy and lactation alters placental growth and leads to sex-specific changes in fetal and neonatal endocrine function. Endocrinology 152 (4), 1378–1387.
Walker, N., Filis, P., O'Shaughnessy, P.J., Bellingham, M., Fowler, P.A., 2019. Nutrient transporter expression in both the placenta and fetal liver are affected by maternal smoking. Placenta 78, 10–17.
Watkins, A.J., Dias, I., Tsuro, H., Allen, D., Emes, R.D., Moreton, J., Wilson, R., Ingram, R.J.M., Sinclair, K.D., 2018. Paternal diet programs offspring health through sperm- and seminal plasma-specific pathways in mice. Proc. Natl. Acad. Sci. U.S.A. 115 (40), 10064–10069.
Wen, X., Triche, E.W., Hogan, J.W., Shenassa, E.D., Buka, S.L., 2011. Association between placental morphology and childhood systolic blood pressure. Hypertension 57 (1), 48–55.
Wilhelm-Benartzi, C.S., Houseman, E.A., Maccani, M.A., Poage, G.M., Koestler, D.C., Langevin, S.M., Gagne, L.A., Banister, C.E., Padbury, J.F., Marsit, C.J., 2012. In utero exposures, infant growth, and DNA methylation of repetitive elements and developmentally related genes in human placenta. Environ. Health Perspect. 120 (2), 296–302.
Williamson, C., Gorelik, J., Eaton, B.M., Lab, M., de Swiet, M., Korchev, Y., 2001. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intra-uterine fetal death in obstetric cholestasis. Clinical science (London, England 100 (4), 363–369, 1979.
Winship, A.L., Gazzard, S.E., Cullen-McEwen, L.A., Bertram, J.F., Hutt, K.J., 2018. Maternal low-protein diet programmes low ovarian reserve in offspring. Reproduction (Cambridge, England) 156 (4), 299–311.
Yang, S.I., Lee, S.H., Lee, S.Y., Kim, H.C., Kim, H.B., Kim, J.H., Lim, H., Park, M.J., Cho, H.J., Yoon, J., Jung, S., Yang, H.J., Ahn, K., Kim, K.W., Shin, Y.H., Suh, D.I., Won, H.S., Lee, M.Y., Kim, S.H., Choi, S.J., Kwon, J.Y., Jun, J.K., Hong, S.J., 2020. Prenatal PM(2.5) exposure and vitamin D-associated early persistent atopic dermatitis via placental methylation. Ann. Allergy Asthma Immunol. : Off. Publ.Am. Coll. Allergy Asthma Immunol. 125 (6), 665–673.e1.
Young, V.B., 2012. The intestinal microbiota in health and disease. Curr. Opin. Gastroenterol. 28 (1), 63–69.
Zhang, B., Liang, S., Zhao, J., Qian, Z., Bassig, B.A., Yang, R., Zhang, Y., Hu, K., Xu, S., Zheng, T., Yang, S., 2016. Maternal exposure to air pollutant PM2.5 and PM10 during pregnancy and risk of congenital heart defects. J. Expo. Sci. Environ. Epidemiol. 26 (4), 422–427.
Zuckerman, B., Frank, D.A., Hingson, R., Amaro, H., Levenson, S.M., Kayne, H., Parker, S., Vinci, R., Aboagye, K., Fried, L.E., et al., 1989. Effects of maternal marijuana and cocaine use on fetal growth. N. Engl. J. Med. 320 (12), 762–768.