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Review Article

Placental Adaptations to Maternal Nutritional Insults as Targets Against the Obesity Epidemic

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Summary: The worldwide obesity epidemic presents a considerable public health and economic challenge globally. While lifestyle and genetic predisposition are recognized obesogenic factors, compelling evidence indicates that maternal nutritional insults (MNI) occurring before pregnancy, during pregnancy, or during lactation predispose the offspring to obesity and other cardiometabolic disorders in adulthood. This phenomenon, termed developmental origins of health and disease (DOHaD) can be utilized to formulate intervention strategies aimed at counteracting the developmental programming of obesity in subsequent generations. The placenta, a temporary organ of pregnancy, experiences adaptive changes in response to MNI. Alterations in placental secretory functions, morphology, and gene expression profiles influence foetal metabolic pathways. The mechanisms by which placental adaptations influence developmental programming offer a distinct opportunity to pinpoint targets for combating the increasing prevalence of obesity. Clinical and experimental studies have clarified various underlying mechanisms, including modified placental metabolic regulation, oxidative stress, inflammation, immune dysregulation, and epigenetic alterations, offering insights for the formulation of effective intervention strategies. This review encapsulates placental adaptive responses to MNI, elucidates the underlying mechanisms, explores potential placental intervention strategies, and identifies areas for future research.

Keywords*: Maternal obesity, intervention, Nutrition, Placenta, DOHaD, developmental programming.*

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INTRODUCTION

Obesity is a prominent yet overlooked public health issue worldwide. Approximately 115 million individuals in developing nations experience obesity-related disorders, with 4 million fatalities occurring each year due to complications associated with overweight and obesity (WHO, 2024). By 2030, approximately 58% of the global population is anticipated to be overweight or obese if prevailing trends persist (Louwen et al., 2024; Chooi et al., 2019). Obesity elevates the risk of various non-communicable disorders, including metabolic syndrome, cardiovascular diseases, type 2 diabetes mellitus, dementia, and cancers, attributable to metabolic dysfunction and chronic cellular inflammation (Rodgers & Sferruzzi-Perri, 2021; Poston et al., 2016).

The swift escalation of obesity rates, particularly in children, suggests a developmental origin, as lifestyle and genetic predisposition alone cannot explain this rapid surge (Louwen et al., 2024). The intrauterine and early postnatal environments significantly influence the long-term health of the offspring (Hales & Barker, 2001; Barker, 1998; Barker, 1995). Maternal overnutrition during these pivotal developmental periods elevate the risk of obesity and other non-communicable diseases in the progeny (Schoonejans & Ozanne, 2021; Louwen et al., 2024). This phenomenon, known as the developmental origins of health and disease (DOHaD), is closely associated with the prevailing obesity rates in numerous populations (Rodgers & Sferruzzi-Perri, 2021; Ganguly et al., 2020).

Maternal nutritional insults (MNI) refer to any suboptimal or adverse nutritional exposure experienced by a woman before pregnancy, during pregnancy or lactation, which can negatively impact foetal development with long-term health risk for the offspring (Marshall et al., 2022; Reynolds & Vickers, 2022). Excessive intake of sugar and fat-containing diets leading to overnutrition; inadequate dietary intake of proteins, carbohydrates, other macro- and micro-nutrients leading to undernutrition; are the causes of MNI (Osendarp et al., 2020). Both maternal overnutrition and undernutrition negatively impact on foetal development through long-term changes in foetal gene expression, organ structure and functions (Zhou et al., 2020). The nutritional status of a pre-pregnant woman can influence oocytes quality, initiating epigenetic changes that may have long term consequences on the offspring developed from such oocytes (Chao et al., 2024). Moreso, the foetus is highly sensitive to maternal nutritional status especially during the critical windows of development (Rodgers & Sferruzzi-Perri, 2021). Maternal nutrition also impacts on the nutritional quality of breast milk, making lactation a critical

window that can impact on infant growth, metabolism and immunity (Favara et al., 2024).

Maternal overnutrition has been reported to significantly contribute to the increase in obesity-related disorders across various populations (Kelly et al., 2020; Rodgers & Sferruzzi-Perri, 2021). Cardiometabolic disorders resulting in over 17 million deaths annually worldwide continue to pose a health challenge despite public awareness and interventions; as these disorders are associated with developmental programming (Louwen et al., 2024). Considering this significant health burden, formulating intervention strategies to mitigate the detrimental effects of MNI on the offspring may decrease the prevalence of obesity and cardiometabolic disorders in the general population.

Maternal overnutrition and undernutrition both expose the developing foetus to nutritional insults that have long-term implications for the offspring health, thus requiring therapeutic interventions as high-risk pregnancies (WHO, 2024; Louwen et al., 2024). At-risk pregnant women encompass those who are overweight, obese, pre-diabetic, or have gestational diabetes, hypertensive, malnourished, or those who adhere to diets high in fats and sugars or low protein diets during the prenatal, antenatal, and postnatal phases (Barker et al., 2001; Rodgers & Sferruzzi-Perri, 2020). The effects of MNI are conveyed through the placenta, disrupting placental metabolic functions. This initiates placental adaptive mechanisms to modulate nutrient delivery to the developing foetus (Vaughan & Fowden, 2016). Recognizing placental adaptive mechanisms to MNI and their influence on programming the offspring for obesity and cardiometabolic disorders later in life, can guide effective interventions. In conjunction with advocacies for nutritious diets and lifestyle modifications, such strategies will mitigate the healthcare and economic impact of obesity on future generations.

EFFECTS OF MATERNAL NUTRITIONAL DEFICIENCIES ON FOETAL METABOLISM

Maternal over-nutrition, typically resulting from excessive fat and sugar consumption, and maternal under-nutrition both represent nutritional adversities to the developing foetus (Louwen *et al*., 2024). While under-nutrition poses a challenge in developing nations, over-nutrition concurrently exists within the same population as a result of westernization and increased availability of energy-dense "junk" foods (Ounjaijean *et al*., 2021). The prevalence of overweight and obese women of reproductive age has significantly escalated alongside the global surge in obesity rates. For example, around 29% of pregnant women in the United States are classified as obese (Driscoll & Gregory, 2021), also 45.7% of pregnant women in Europe were categorized as overweight or obese in 2019 (European Commission, 2019). Obesity and overweight stem from an imbalance between energy consumption and expenditure, characterized by a body mass index (BMI) of ≥30 kg/m² for obesity and 25–29.9 kg/m² for overweight (Kearns & Reynolds, 2024).

Maternal obesity is nutritionally detrimental to the developing foetus as it increases maternal concentrations of lipids, glucose, adipokines, insulin-like growth factors, pro-inflammatory markers and cytokines, which crosses through the placenta to the foetus (Louwen *et al*., 2024). As shown in Figure 1, elevated adipose tissues produce additional adipokines and growth factors, triggering pro-inflammatory and immune responses that disrupt foetal metabolic processes (Louwen *et al*., 2018; Scheja & Heeren, 2019). Pro-inflammatory metabolites from the maternal circulation traverse the placental barrier into foetal circulation, initiating a series of events that lead to foetal hyperglycaemia and hyperlipidemia (Kelly *et al*., 2020). Maternal metabolic and inflammatory signals significantly influence placental function, thus establishing an obesity-prone metabolic environment for the developing foetus (Vaughan *et al*., 2017). While the various mechanisms through which maternal nutritional imbalances predispose the developing foetus to obesity and other cardiometabolic disorders have not been fully elucidated, substantial evidence has distinctly identified the placenta as a conduit for transmitting compromised maternal metabolic signals to the foetal environment (Ogunsola *et al*., 2019; Ganguly *et al*., 2020; Louwen *et al*., 2024).

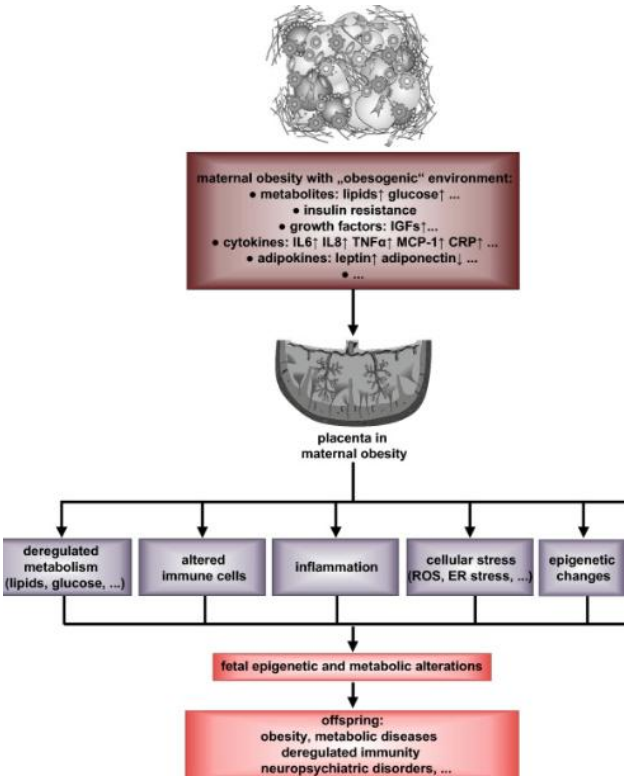

Figure 1:
Placenta as an axis linking maternal obesity to adverse offspring outcomes. Maternal obesity and other MNI creates an "obesogenic" intrauterine environment due to excess nutrients, insulin resistance, altered cytokines and adipokines levels. The placenta adapts to these maternal nutritional insults by developing defects in its nutrient metabolism, immune regulation, inflammation, cellular stress and epigenetic modifications (Adapted from Louwen *et al.,* 2024).

DEVELOPMENTAL PROGRAMMING OF OBESITY RESULTING FROM MATERNAL NUTRITIONAL DEFICIENCIES

The developmental origins of health and disease (DOHaD), or developmental programming, is a phenomenon initially described by Barker *et al*. (1995), wherein foetal exposure to detrimental intrauterine conditions modifies foetal metabolism, resulting in long-term health implications (Schoonejans & Ozanne, 2021). These metabolic changes

impair foetal development, leading to adaptive mechanisms that subsequently predispose the offspring to metabolic and cardiovascular diseases in later life (Ganguly *et al*., 2020). Variations in maternal nutrient availability and placental hormones during crucial phases of foetal development can modify foetal gene expression, resulting in enduring alterations in various foetal physiological functions and structures (Poston *et al*., 2016). The DOHaD hypothesis elucidates the physiological adaptations that the foetus experiences in response to either an excess or deficiency of metabolic substrates during prenatal, antenatal, and early postnatal periods, resulting in long-term detrimental health consequences.

Literature indicates that maternal nutritional insults (MNI), whether preconceptional, during gestation, or while breastfeeding, predisposes the foetus to obesity and other cardiometabolic disorders in later life (Ogunsola *et al*., 2019; Ganguly *et al*., 2020; Louwen *et al*., 2024). Studies by Schoonejans and Ozanne (2021) showed that children of obese mothers exhibited increased body weight and total fat mass, independent of genetic or postnatal influences. The children born after maternal weight loss had reduced body weights, fat mass, and insulin resistance compared to their siblings born prior to maternal weight loss, despite being on a comparable postnatal diet. Children born to these obese women had an elevated risk of developing metabolic syndrome during both childhood and adulthood.

These results exemplify the DOHaD phenomenon, indicating that foetal metabolism adjusts to maternal nutritional availability *in utero*; however, when the progeny encounter a divergent nutritional environment postnatally, the intrauterine adaptations lead to metabolic dysfunction. Consequently, maternal nutrition during the prenatal, antenatal, and postnatal periods influences the offspring health in both the short and long term.

Numerous clinical studies have established correlations between diverse maternal nutritional deficiencies and negative outcomes in the offspring (Chooi *et al*., 2019; Inoue *et al*., 2018; Poston *et al*., 2016; Blackmore & Ozanne, 2015). Nevertheless, there is a paucity of information regarding the mechanisms underlying these outcomes. Experimental investigations utilizing animal models of MNI have however clarified certain mechanisms implicated in DOHaD. The recognized mechanisms encompass modifications in metabolic and signalling pathways, inflammation, oxidative stress, and epigenetic alterations (Ganguly *et al*., 2020; Schoonejans & Ozanne, 2021). These mechanisms which have also identified the placenta as the exclusive channel for communicating disrupted maternal metabolic signals to the foetal environment can be investigated to formulate intervention strategies aimed at mitigating the intergenerational transmission of MNI-related cardiometabolic disorders (Louwen *et al*., 2024).

Maternal nutritional deficiencies can be induced in laboratory animals through various methodologies. Researchers have induced MNI in laboratory animals predominantly by altering the maternal diet to replicate Western dietary patterns (Schoonejans & Ozanne, 2021; Alfaradhi *et al*., 2011; Taylor *et al*., 2005). These dietary interventions may be implemented prior to pregnancy, during pregnancy, and/or during lactation (Beeson *et al*., 2018). Typical experimental MNI diets consist of high-fat diets, high-sugar diets, or a combination of both high fat and high sugar (Ferey *et al*., 2019; Stanford *et al*., 2015). Animal models of diet-induced MNI also result in insulin resistance or glucose intolerance, frequently leading to gestational diabetes mellitus as well (Ogunsola *et al*., 2019; Louwen *et al*., 2024). Experimental models of maternal hyperglycaemia or type 2 diabetes mellitus also elucidate the impact of developmental programming, as the foetus is subjected to elevated maternal glucose concentrations *in utero*. Other models that exemplify DOHaD are the genetically modified obesity models, such as leptin receptor heterozygous dams, which replicates an intrauterine environment characterized by obesity or insulin resistance (Poston *et al*., 2016; Schoonejans & Ozanne, 2021). However, these genetic models possess restricted translational significance as human obesity is predominantly attributed to nutritional factors.

A high-fat diet administered to rats prior to and during gestation elevated plasma triglyceride levels in the offspring, indicating a diminished ability to store lipids (Dearden *et al*., 2020). This disruption in energy homeostasis during foetal development was associated with increased adiposity in the progeny (Schoonejans & Ozanne, 2021). In another study, maternal obesity led to offspring body weight gain and increased adipose tissue mass in rats. Subsequently, the progeny was transitioned after weaning to either a control diet or a high-fat diet (HFD). The detrimental impacts of maternal obesity and a postnatal high-fat diet were cumulative, resulting in offspring on the high-fat diet exhibiting the highest levels of adiposity. Also, the progeny of obese mothers fed on control diet after weaning, exhibited greater adiposity compared to the progeny of non-obese rats. Adipose tissue hypertrophy was associated with obesity programming in these progenies (Chang *et al*., 2019).

Paternal obesity contributes to developmental programming; however, foetal exposure to an obesogenic intrauterine environment exerts a more significant influence on foetal metabolism than paternal obesity, as modifications in maternal metabolism directly affect the foetus through the placenta (Chang *et al*., 2019).

ROLE OF THE PLACENTA IN THE DEVELOPMENTAL PROGRAMMING OF OFFSPRING OBESITY

Trophoblast cells in human pregnancy commence differentiation into the placental tree-like structures approximately on day 21 post-fertilisation (Turco & Moffett, 2019). The placenta is a temporary organ of pregnancy which connects maternal and foetal circulation. It functions to facilitate nutrient transport, gaseous exchange, metabolic waste elimination, and hormone synthesis, necessary for foetal growth and development (Burton & Fowden, 2015; Kreis *et al*., 2020). The human placenta comprises the chorionic plate (foetal side) and basal plate (maternal side) and possesses the ability to activate molecular pathways to safeguard the developing foetus (Bayer *et al*., 2016; Kreis *et al*., 2020). These molecular pathways regulate placental development and functions (Knofler *et al*., 2019). Studies have shown that modifications in placental function such as secretory functions, morphology, and gene expression (Figure 1),

influence fetal growth and development, resulting in both immediate and prolonged effects on offspring health (Schoonejans & Ozanne, 2021; Isganaitis *et al*., 2014; Howie *et al*., 2009).

The placenta undergoes morphological and functional adaptations in response to maternal obesity to regulate nutrient transfer to the developing foetus (Louwen *et al*., 2024). However, these placental adaptations may induce enduring structural and functional alterations in the foetus as a consequence of these modifications (Inoue *et al*., 2018; Renshall *et al*., 2020). Despite the stringent regulation of placental structure, trophoblast giant cells (TGCs) maintain direct contact with maternal circulation, thus modulating maternal-foetal blood flow and synthesis of placental hormones (Ganguly *et al*., 2020; Phillips *et al*., 2017; Curtis *et al*., 2014). Spongiotrophoblast cells, situated between the trophoblast giant cells and the inner labyrinth layer, offer structural support and regulate endothelial proliferation (Goulopoulou & Davidge, 2015). Glycogen cells within the spongiotrophoblast layer migrate into the decidua and aggregate around maternal spiral arteries. The glycogen cells proliferate in response to increased maternal glucose levels, substantially augmenting placental glycogen reserves and increasing glucose availability for foetal utilisation. This development subsequently leads to foetal overgrowth and macrosomia (Ganguly *et al*., 2020; Ogunsola *et al*., 2019).

PLACENTAL ADAPTIVE RESPONSES TO MATERNAL NUTRITIONAL DEFICIENCIES

The placenta selectively facilitates the transfer of nutrients and other substances from maternal to foetal circulation (Burton & Fowden, 2015). This selectivity is crucial, as the foetus depends entirely on the placenta to manage its nutrient supply and blood circulation (Louwen *et al*., 2024). The placenta undergoes significant metabolic activity to perform these functions. Maternal obesity and other nutritional disturbances modify placental metabolic functions, as alterations in maternal nutritional status activate placental adaptive mechanisms to modulate nutrient transfer to the foetus (Vaughan & Fowden, 2016). Experimental and clinical investigations have elucidated various mechanisms through which the placenta adjusts to maternal nutritional deficiencies, resulting in metabolic programming in the progeny. These mechanisms include:

1. **Dysregulation of Placental Metabolism**: Glucose serves as the primary substrate for foetal and placental energy metabolism (Louwen *et al*., 2024). Glucose is transferred from maternal to foetal circulation down a concentration gradient and is regulated by placental GLUT transporters. Maternal obesity modifies the expression of glucose transporters, resulting in dysregulated placental glucose metabolism (Barbour-Tuck *et al*., 2018). Maternal lipid levels are physiologically elevated compared to the non-pregnant state, however maternal obesity further exacerbates these levels (Hellmuth *et al*., 2017). Alterations in maternal lipid metabolism disrupt placental metabolic processes and are conveyed to the foetal circulation (Louwen *et al*., 2024). Maternal fatty acids traverse to the foetus circulation, facilitated by placental membrane fatty acid transport proteins that are responsive to maternal nutritional status (Hellmuth *et al*., 2017). Elevated maternal lipid levels are reported to impair the expression and functions of placental fatty acid transport proteins (Howell & Powell, 2017). Rosario *et al*. (2020) established that maternal obesity enhances the expression of placental fatty acid transporters FATP2 and FATP6, resulting in increased lipid transfer and accumulation in the foetal circulation. Diaz *et al*. (2023) similarly indicated that maternal high-fat diets elevate placental expression of genes associated with lipid transport.

A study using mice have demonstrated that maternal HFD-induced obesity enhanced placental transport of amino acids and glucose to the foetus and activated placental insulin and mTOR signalling pathways, resulting in foetal overgrowth (Rosario *et al*., 2015). The regulation of placental nutrient transport is facilitated by the mTOR pathways, underscoring its role in both placental nutrient transport and foetal development (Rosario *et al*., 2016a; Rosario *et al*., 2016b). Elevated maternal lipid concentrations can alter the functions of placental amino acid transporters through the Toll-like receptor 4 (TLR4) signalling pathway (Howell & Powell, 2017). The expression of placental TLR4 is usually elevated during pregnancy; however maternal obesity further increases its expression which was positively correlated with maternal and placental IL-6 levels (Yang *et al*., 2016; Thaete *et al*., 2013). These findings suggest that increased placental TLR4 expression enhances placental nutrient transfer capacity, resulting in foetal overgrowth and adiposity in the progeny.

2. **Placental Inflammatory Responses to MNI and Maternal Obesity**: Diet can modify maternal metabolite concentrations with a direct impact on trophoblastic intracellular signalling pathways (Louwen *et al*., 2024; Kearns & Reynolds, 2023). This is because spongiotrophoblasts express glucose transporters (GLUTs) as well as receptors for leptin, insulin, and IGF-1 (James-Allan *et al*., 2019; Ebenbichler *et al*., 2002). Studies have identified unique inflammatory gene expression profiles in the placenta (Braun *et al*., 2022; Olney *et al*., 2022; Myatt *et al*., 2016). This finding corroborates the diminished resistance to infection and an inadequate immune response observed in the offspring of mothers who consumed high-fat or high-sugar diets during pregnancy through pro-inflammatory mechanisms (Louwen *et al*., 2024; Myles *et al*., 2013). Elevated maternal metabolite levels trigger inflammatory responses by activating placental Toll-like receptor 4 (TLR4) and receptors for advanced glycation end-products (Shirasuna *et al*., 2016; Gregor *et al*., 2011). The pro-inflammatory state elevates reactive oxygen species (ROS) and pro-inflammatory cytokine concentrations, which has been reported to modify the phenotype of foetal immune cells and possibly induce epigenetic alterations in the progeny (Pantham *et al*., 2015). Elevated levels of pro-inflammatory cytokines, namely IL-6 and TNF-α are reported to enhance placental System A amino acid transport (Howell & Powell, 2017), suggestive that placental inflammatory responses increase placental nutrient transport capacity. Interleukin-6 can enhance fatty acid uptake in trophoblast cells, leading to excessive fat accumulation in the offspring of obese mothers. TNF-α similarly enhances trophoblast System A transport through p38 MAPK signalling, indicating that pro-inflammatory

cytokines can modify placental function through various pathways (Howell & Powell, 2017).

3. **Dysregulation of Placental Immunity**: The immune system plays a crucial role during pregnancy which include foetal allograft acceptance and its protection from foreign substances throughout foetal development (Louwen *et al*., 2024). The placenta harbours immune cells (e.g., macrophages, mast cells, dendritic cells, and natural killer cells) that serve to protect the developing foetus from pathogens that may cross from the maternal circulation (Fass & De Vos, 2018). Maternal obesity however has been shown to further increase placental macrophage accumulation within the villous stroma, fostering inflammation, oxidative stress, and metabolic dysregulation (Mele *et al*., 2014). In a study by Laskewitz *et al*., (2019), the placentas of obese women were shown to exhibit an elevated ratio of pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. M1 Macrophages generate pro-inflammatory cytokines, resulting in placental inflammation usually evidenced by placentomegaly (Ogunsola *et al*., 2014). Under normal circumstances, the placenta functions to promote an anti-inflammatory maternal-foetal environment; however, maternal obesity or gestational diabetes mellitus alters this placental function to favour a pro-inflammatory maternal-foetal milieu (Louwen et al., 2024).

4. **Placental Oxidative Stress**: The increase in metabolic rate during early pregnancy is associated with some oxidative stress required to facilitate cell differentiation and angiogenesis (Louwen *et al*., 2024). However, maternal obesity or poor dietary choices can induce excessive reactive oxygen species production, thereby diminishing the overall antioxidant capacity during pregnancy (Al-Gubory *et al*., 2010). This development disturbs placental cellular homeostasis, resulting in increased oxidative stress that may harm placental cellular constituents (Kearn & Reynolds, 2023). Studies have indicated elevated levels of nitric oxide and superoxide dismutase (SOD) in maternal circulation of obese women, while the placental homogenates likewise exhibited enhanced glutathione and SOD activity (Louwen *et al*., 2024). Placental oxidative stress impairs mitochondrial function, specifically through the uncoupling protein 2 (UCP2) and sirtuin 1 (SIRT1) genes up-regulation (Martino *et al*., 2016). Increased placental oxidative stress disrupts endoplasmic reticulum homeostasis and activates the unfolded protein response (UPR) (Brombach et al., 2022). The UPR initially aims to restore protein-folding balance, however, its chronic activation triggers inflammation and impairs nutrient-transport and hormone synthesis (Fowden et al., 2022). UPR pathways then recruit stress kinases like JNK and NF-κB, fuelling placental cytokine release and metabolic dysfunction (Shen et al., 2023). These UPR-driven changes reshape the intrauterine environment, exposing the foetus to excess fuels and inflammatory signals (Brombach et al., 2022). This altered placental milieu programs foetal metabolism and energy regulation, thus increasing offsprings' risk for obesity and cardiometabolic disorders in adulthood (Zhang et al., 2022).

5. **Epigenetic Modifications in the Placenta**: Epigenetic modifications are alterations in DNA conformation that do not change the genetic code (Salvatore Lacagnina, 2019). Nutritional deficiencies prior to or during pregnancy and lactation can affect foetal gene function through DNA methylation (Shrestha *et al*., 2020). These phenotypic alterations arise from adaptive mechanisms in the foetus in expectation of a comparable nutritional milieu after delivery. However, a difference in postnatal nutritional status leads to a mismatch with the nutritional environment the foetus had adapted to during intrauterine life, resulting in a thrifty phenotype (Myatt & Maloyan, 2016; Barker, 2004). Maternal obesity and gestational diabetes mellitus have been linked to changes in placental DNA methylation (Fernandez-Jimenez *et al*., 2022). For instance, the genes involved in the adiponectin pathway, specifically adiponectin receptor 1 (ADIPOR1), leptin (LEP), and the leptin receptor (LEPR), exhibit differential methylation in the placental tissues of obese women (Nogues *et al*., 2019). Alterations in placental DNA methylation have been reported in women who were obese prior to pregnancy and in those who experienced excessive gestational weight gain attributable to dietary factors (Shrestha *et al*., 2020). A study identified 27 placental CpG sites exhibiting differential methylation in obese women (Fernandez-Jimenez *et al*., 2022). Another study identified 104 CpG sites (annotating 97 genes) which exhibited differential methylation associated with increased gestational weight gain (Gomez-Vilarrubla *et al*., 2023). Multiple placental CpG sites (e.g., FRAT1, SNX5, KCNK3) correlated with detrimental metabolic phenotypes in the progeny of obese women (Gomez-Vilarrubla *et al*., 2023).

PLACENTA-FOCUSED STRATEGIES TO COMBAT THE OBESITY EPIDEMIC

Recent studies have focused on creating interventions and therapeutic strategies aimed specifically at the placenta, as it serves as the primary channel for transferring disrupted maternal metabolic signals to the foetus (Ganguly *et al*., 2020). These strategies seek to enhance placental function, as numerous pregnancy complications and negative offspring outcomes are associated with placental dysfunction. Substances transported from the maternal circulation to the foetal circulation through the placenta or synthesised by the placenta influence foetal development (Phillips *et al*., 2017). However, not all foetuses subjected to a detrimental intrauterine environment exhibit adverse health outcomes, attributable to placenta's effective adaptive barrier function (Ganguly *et al*., 2020). This distinctive placental characteristic can be explored to avert the developmental programming of obesity and other cardiometabolic conditions. In the formulation of pregnancy interventions, the safety of both the mother and the foetus must be prioritized. Despite the limited number of studies, some have utilized methods such as placenta-targeted liposomes and nanoparticles to enhance placental and foetal outcomes in pregnancies complicated by obesity, diabetes, and hypertension. Some of these placental intervention approaches are discussed below.

1. **Liposomes Targeted to the Placenta**: Liposomes are phospholipid nanocarriers employed for targeted drug delivery (King *et al*., 2016). Conjugating tumour-specific peptides to the liposome surface facilitates the targeted delivery of therapeutic agents to specific organs

(Harris, 2016). The placenta exhibits numerous physiological and biochemical characteristics akin to tumours: it generates new blood vessels, proliferates swiftly, eludes immune detection, and infiltrates healthy tissue (the uterine wall). It additionally expresses tumour-homing peptides that specifically target integrin receptors (Ganguly *et al*., 2020; Holtan *et al*., 2009). King *et al*. (2016) illustrated that tumour-targeting peptide-coated liposomes serve as nanocarriers for precise drug delivery to the placenta in both mice and humans. These liposomes specifically adhere to the labyrinth region of the mouse placenta, accumulating in the outer syncytiotrophoblasts and maternal decidual spiral arteries, without adhering to the junctional zone or penetrating the underlying cytotrophoblast layer – foetal circulation (Ganguly *et al*., 2020). The placenta-targeted peptide-coated liposomes exhibited no adverse effects in pregnant wild-type mice, indicating their safety and efficacy for use during gestation (Cureton *et al*., 2017). Consequently, peptide-coated liposomes present a promising approach for targeted therapeutic delivery to the placenta as shown in Table 1.

2. **Placenta-Targeted Nanoparticles:** Nanoparticle carriers can transport substances to targeted organs with prolonged release (Cureton *et al*., 2017). Encapsulation of therapeutic agents within nanoparticles inhibits drug degradation, prolongs the drug's half-life, and enhances bioavailability at the target organ (Ganguly *et al*., 2020). Research has employed polymeric nanoparticles to selectively target the placenta (Phillips *et al*., 2017). The placental syncytiotrophoblasts efficiently absorbs nanoparticles owing to their considerable size and negative charge, thereby diminishing the phagocytic clearance of the drug.

Table 1:
Summary of placental adaptive responses to maternal obesity or MNI, the underlying mechanisms, and potential placenta-targeted interventions.

Placental Response to Obesity & MNI	Mechanisms	Placenta-targeted Interventions	References
Metabolic Dysregulation	Placental nutrient transporters (GLUTs for glucose, FATPs for fatty acids) are upregulated and growth pathways (insulin/ mTOR) activated, leading to excessive nutrient delivery to the foetus.	Placenta-targeted liposomes: Peptide-coated liposomal nanocarriers can selectively deliver therapeutic agents to placental tissue, improving placental function without crossing to the foetal circulation.	King *et al*., 2016.
Pro-inflammatory Response	Chronic placental inflammation triggered via nutrient-induced Toll-like receptor (TLR4) activation. Elevated placental pro-inflammatory cytokines further stimulate nutrient transport to the foetus and promote fat accumulation in foetal tissues.	Resveratrol: A polyphenol with anti-inflammatory effects inhibits NF-κB signalling, which reduces placental cytokine expression in explant studies and decrease offspring adiposity in obese rodent models. Curcumin: An anti-inflammatory compound from turmeric activates PPAR-γ, suppressing pro-inflammatory pathways. In vitro, curcumin inhibit adipocyte differentiation, suggesting potential to limit foetal fat programming.	Ganguly *et al.*, 2020; Peng *et al*., 2021.
Immune Dysregulation	Increased pro-inflammatory M1 phenotype and accumulation in villous tissue leading to placental inflammation and oxidative stress. High M1/M2 macrophage ratios and their cytokines lead to placentomegaly and dysfunction.	Omega-3 fatty acids: rebalance placental immune responses by reducing M1 macrophage activation and cytokine release (as evidenced by lowered IL-6, TNF-α in placenta with fish oil administration). General anti-inflammatory strategies: Improved maternal diet and reduction of obesity before/during pregnancy. (No placenta-specific immune drug is established yet).	Louwen *et al*., 2024; Ramalingam *et al*., 2021.
Oxidative Stress	Increased reactive oxygen species and overwhelmed antioxidant defences. Upregulated oxidative stress genes (e.g. UCP2, SIRT1) and activation of the unfolded protein response, linking oxidative damage to later offspring obesity.	Green tea polyphenols: An antioxidant flavonoid enhances antioxidant capacity, leading to improved insulin sensitivity and reduced fat accumulation in offspring. Placenta-targeted antioxidants: Experimental therapies aimed at delivering antioxidants or oxidative stress inhibitors directly to the placenta e.g. via nanoparticles are being explored.	Martino *et al*., 2016; Kearns and Reynolds., 2022.
Epigenetic Modifications	Altered DNA methylation of genes that regulate metabolism. Differential methylation of placental genes (e.g. adiponectin and leptin signalling genes) as specific placenta DNA methylation patterns (at numerous CpG sites) correlate with offspring's later metabolic dysfunction, indicating epigenetic programming of obesity risk.	No established therapy yet: research focus is on preventing these changes by improving placental environment. Emerging strategies: Future therapies might include epigenetic modulators delivered to the placenta to protect the foetus from obesogenic gene expression changes.	Salvatore Lacagnina, 2019; Louwen *et al*., 2024.

3. **Nutritional Interventions against Placental Inflammation**

i. **Eicosapentaenoic and Docosahexaenoic Acids (Fish Oil):** Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil possess anti-inflammatory properties that may mitigate the developmental programming of obesity in the offspring of obese mothers (Kearns & Reynolds, 2024). In vitro, treatment with fish oil on placental tissue reduced the expression of genes associated with lipogenesis, adipogenesis, and fatty acid β-oxidation (Isesele *et al*., 2022). Haghiac *et al*. (2015) discovered that pregnant women consuming fish oil supplements exhibited diminished placental and adipose expression of IL-6, IL-8, TNF-α, and TLR4. Satokar *et al*. (2023) documented a 17% decrease in fasting triglycerides among women who ingested fish oil during gestation. Maternal fish oil supplementation also enhanced insulin sensitivity in the progeny of rats subjected to a high-fructose diet (Ramalingam *et al*., 2021; Satokar *et al*., 2022). However, Ramalingam *et al*. (2021) noted several adverse effects namely elevated adipokine levels, diminished Mcp1 and TNFα gene expression in female progeny, accompanied by increased body weight and fat mass. The method used for the fish oil administration may affect their findings. In that study, fish oil was incorporated into the feed (potentially leading to fatty acid oxidation), while studies by Satokar *et al*. (2022) delivered fish oil independently, thereby averting oxidation. These findings indicate that fish oil supplementation should be directed towards pregnant women with metabolic disorders, as it may not confer advantages for all pregnancies.

ii. **Resveratrol:** Resveratrol is a polyphenolic compound found in grapes, berries, and peanuts. It exhibits anti-inflammatory properties by inhibiting the NF-κB pathway, a principal regulator of inflammation, and diminishing cyclooxygenase activity (Zhou *et al*., 2018). Ros *et al*. (2018) demonstrated that maternal resveratrol intake diminished offspring body weight and visceral adipose tissue in Wistar rats. Although limited information exists regarding the effects of resveratrol during human pregnancy, resveratrol treatment of human placental explants diminished the expression of inflammatory cytokines (IL-6, IL-1β, IL-1α, MCP-1) (Tran *et al*., 2017). Resveratrol exhibits anti-inflammatory properties in adipose tissue, which may be utilized to enhance outcomes in pregnancies affected by obesity (Ganguly *et al*., 2020).

iii. **Curcumin:** Curcumin is a polyphenolic compound found in turmeric that possesses anti-inflammatory properties by its modulation of pro-inflammatory signalling pathways, such as the activation of peroxisome proliferator-activated receptor γ (Peng *et al*., 2021). Its anti-inflammatory properties are recognized for their efficacy in managing metabolic syndrome (Panahi *et al*., 2016). In vitro, curcumin inhibits adipocyte differentiation, indicating its potential to diminish adipose tissue formation during foetal development (Jin *et al*., 2018).

iv. **Epigallocatechin Gallate:** Epigallocatechin gallate (EGCG) is a bioactive flavonoid found in green tea. In vitro, EGCG impedes preadipocyte differentiation and lipogenesis, while facilitating adipocyte apoptosis and fatty acid β-oxidation through protein kinase signalling pathways (Li *et al*., 2018). EGCG supplementation enhanced insulin-sensitizing markers and diminished retroperitoneal fat in the progeny of obese, high-fat-fed mice (Li *et al*., 2012). Hachul *et al*. (2018) discovered that adult progeny of mothers administered green tea extract exhibited enhanced glucose tolerance; however, a postnatal high-fat diet increased their adipose tissue mass irrespective of maternal supplementation.

AREAS FOR FURTHER RESEARCH AND RECOMMENDATIONS

Additional research is required to clarify the molecular mechanisms that govern placental adaptive responses to maternal obesity and other nutritional adversities. Animal models, human trophoblast stem cells, and placental organoids can be utilized to examine the impact of maternal obesity and other maternal nutritional imbalances on placental function. Such studies will facilitate the formulation of secure and accurate interventions to avert epigenetic and metabolic programming in the progeny. Future placenta therapies may involve the administration of epigenetic modulators to the placenta to safeguard the foetus from alterations in gene expression.

Awareness on the role of diet on oocyte quality to adolescent girls and pre-pregnant women, integration of maternal nutrition into national food and health security policies, and the study of indigenous foods and their roles in mitigating maternal nutritional insults are recommended to effectively combat the menace of obesity in the general population.

CONCLUSION

Placental adaptations to maternal obesity and other metabolic nutritional imbalances elucidate a crucial mechanism by which maternal obesity and other metabolic nutritional disturbances affect offspring health. These adaptive modifications, although initially meant to safeguard the foetus, predispose the progeny to obesity and other cardiometabolic disorders in later life. Increasing evidence highlights the necessity for specific interventions that can influence placental function to avert the transgenerational transmission of metabolic disorders. Placenta-targeted therapeutic strategies summarised in Table 1 present promising opportunities to reverse or alleviate the detrimental effects of maternal obesity. As the global obesity epidemic escalates, comprehending the crucial function of the placenta in developmental programming becomes increasingly vital. By implementing early interventions and emphasizing placental health, the cycle of intergenerational obesity can be disrupted, fostering a healthier future generation

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