Placenta and Reproductive Medicine

REVIEW ARTICLE

YOUNG INVESTIGATOR CORNER

Maternal obesity-related placental dysfunction: From peri-conception to late gestation

Emmanuel Amabebe[1,#], Nadia M Ikumi[2,#], Komala Pillay[2], Mushi Matjila[3], Dilly OC Anumba[1]

[1]Department of Oncology and Metabolism, University of Sheffield, Sheffield S10 2SF, UK;
[2]Division of Anatomical Pathology, Department of Pathology, University of Cape Town, Cape Town, South Africa;
[3]Department of Obstetrics and Gynaecology, University of Cape Town, Cape Town, South Africa

Abstract

Obesity is a global epidemic with alarmingly high prevalence rates worldwide. The increasing incidence of obesity among reproductive age women, which progresses to obesity in pregnancy is of particular concern. A successful pregnancy is dependent on the balanced interaction between maternal cardiometabolic function, genetic predisposition, and optimal placental development. Maternal obesity, both pre-pregnancy and gestational, has been associated with adverse outcomes including poor fetal development, stillbirth, preterm birth, and metabolic complications later in life. To gain a more comprehensive understanding of the mechanistic interplay of key mediators of obesity-associated placental dysfunction and adverse pregnancy outcomes, we conducted a review of 24 studies that investigated placental dysfunction and maternal obesity retrieved from MEDLINE, LILACS and EMBASE. The findings demonstrate that maternal obesity is a well-established risk factor for poor placental function. Pre-pregnancy obesity alters the placental transcriptome. Maternal obesity during gestation induces changes in placental morphology, dysregulated placental metabolism, inflammation and oxidative state, as well as endothelial dysfunction. There is also clear evidence that maternal obesity is associated with altered placental angiogenesis/vascularisation which increases the risk of early-onset preeclampsia. Studies show a link between maternal obesity and increased placental vascular disorders, placental weight, placental volume and birth weight. These obesity-related placental disorders are often associated with insulin resistance and gestational diabetes mellitus.

Key words: maternal obesity, placenta, pregnancy, insulin resistance, gestational diabetes mellitus, preeclampsia

INTRODUCTION

Obesity—body mass index (BMI) ≥ 30 kg/m^2, is a global epidemic with alarmingly high prevalence rates worldwide. World Health Organization (WHO) data shows that obesity rates tripled from 1975 to 2016, and as at 2016, there were more than 650 million obese adults, over 18 years and older, globally.[1] A major concern is the increase in obesity in women of reproductive age, which leads to obesity in pregnancy or maternal obesity (MO).

The prevalence rates of MO across Africa range from 17.9% in the first trimester to 6.5%–50.7% in the third trimester.[2] MO rates > 40.0% have been reported in sub-Saharan Africa.[2,3] In Asia, the prevalence of MO has been reported to be over 20.0% in Malaysia and even higher than 40.0% in India.[4,5] The prevalence of MO is over 20.0% in Europe,[6,7] while the prevalence of obesity in reproductive age women is at least 31.8% in the United States of America.[8]

The placenta, though transient, has been described as the

Peer review under responsibility of the Editorial Board.
[#]These authors contributed equally to this work.
Corresponding Author:
Dr. Emmanuel Amabebe, E-mail: e.amabebe@sheffield.ac.uk; https://orcid.org/0000-0002-3924-5270

Citation:
Amabebe E, Ikumi NM, Pillay K, Matjila M, Anumba DOC. Maternal obesity-related placental dysfunction: From peri-conception to late gestation. *Placenta Reprod Med*. 2023;2:9.

DOI: 10.54844/prm.2023.0361

Received: 07 March 2023
Accepted: 25 April 2023
Published: 18 July 2023

This article was submitted to Young Investigator Corner, a section of the journal *Placenta and Reproductive Medicine* (PRM).

most important organ in the body as it performs functions that are subsequently assumed by multiple organs including the liver, gut, lungs, kidneys and endocrine glands.[9] Its major function is to supply oxygen and nutrients to the fetus. It also regulates maternal metabolism to accumulate sufficient energy reserves initially and subsequently transferring the nutrients to support fetal growth in later gestation and lactation post-natally.[9]

MO is a well-established risk factor for poor placental function as well as obstetric and birth complications.[10] These include preeclampsia, fetal growth restriction (FGR), preterm birth (PTB), and caesarean delivery.[3,11,12] Obesity is also characterized by low-grade systemic inflammation, altered gut microbiota, insulin resistance and hyperglycemia, which are metabolic syndrome-like features similar to those seen in diabetes mellitus.[13] MO and associated inflammation and insulin resistance can, therefore, lead to gestational diabetes mellitus (GDM) and consequently placental dysfunction.[13] Obese mothers with GDM are three times more likely to have large for gestational age (LGA) or macrosomic deliveries.[14] The downstream effect particularly for LGA or macrosomic babies is an increased likelihood to develop childhood obesity and metabolic disease later in life.[15]

The effects of obesity are not only limited to the gestational period. Obesity is also a disruptor of female fertility affecting ovulation and endometrial function. Hence, weight loss in women with obesity has been linked to improved fertility, particularly in those with polycystic ovarian syndrome-associated anovulatory infertility.[16,17]

A successful pregnancy is dependent on a balanced interaction between maternal cardiometabolic functioning, genetic predisposition and optimal placental development and function.[18] How MO affects placental development/function is still poorly understood. It is against this background that we conducted a review of findings from studies on the impact of MO on placental function, consolidating data from the peri-conceptional period through to late gestation. This is particular important due to the increasing need for improved understanding of the mechanisms underlying placental dysfunction in obese mothers which may consequently impact fetal development, birth and postnatal life.

This review therefore seeks to explore various mechanisms that underpin the association of MO with poor placental development and function. Whether obesity (in the absence of insulin resistance and GDM) can disrupt placental function was also examined. Specifically, this review seeks to address whether: (a) there is causal effect of MO on placental dysfunction; (b) pre-pregnancy BMI plays a role in the association; (c) the impact of MO on placental dysfunction is gestation-specific; and (d) there are specific parts or functions of the placenta that are most susceptible.

METHODS

Identification of studies

A review of literature was conducted on studies published on placental dysfunction associated with MO between 1997 and 2023. The published papers were extracted from MEDLINE, LILACS and EMBASE. We applied the search strategy using the keywords, "maternal obesity", "overweight", "placenta", "placenta diseases", "pregnancy complications" and "birth outcome". Boolean operators "AND" and "OR" were applied and we included papers published in English.

Inclusion criteria

We included full text and English language (including foreign language articles pre-translated by the publisher) publications presenting research results on obesity, the human placenta and pregnancy complications. We also included studies that explored the association or impact of pre-pregnancy obesity on maternal pregnancy and birth outcomes. Our selection of studies included randomized controlled trials, observational studies (including case-control and cohort studies), and clinical trials including Phase I – IV trials. *Ex vivo* and *in vitro* studies with human placental tissues were also included.

Exclusion criteria

We excluded studies that were: duplicates, literature reviews, case reports, studies that were not relevant to our search including studies with no investigations on obesity, studies that had no data on the human placenta or study protocols without definite outcomes or conclusions yet. We further excluded studies that were not published in English or had no English translated version available.

Data extraction

The initial search was conducted by one investigator (NI) and validated by a secondary conductor (EA) to ensure accuracy of the search and application of inclusion and exclusion criteria. The co-authors participated in the selection of the studies for inclusion and reviewed the full text of articles included in this review. The process of study selection and exclusion is presented on a flowchart (Figure 1).

RESULTS

Table 1 describes the characteristics of the included studies (n = 24) arranged chronologically from the most recent to the earliest according to the inclusion/exclusion criteria and grouped into five sub-sections. Two of the studies were randomized controlled trials, 3 were *ex vivo*/*in vitro* mechanistic studies, while 19 were observational studies including case-controls (n = 2) and cohort (n = 17) studies.

Pre-pregnancy and peri-conception obesity

The lone study[19] included in the pre-pregnancy and peri-

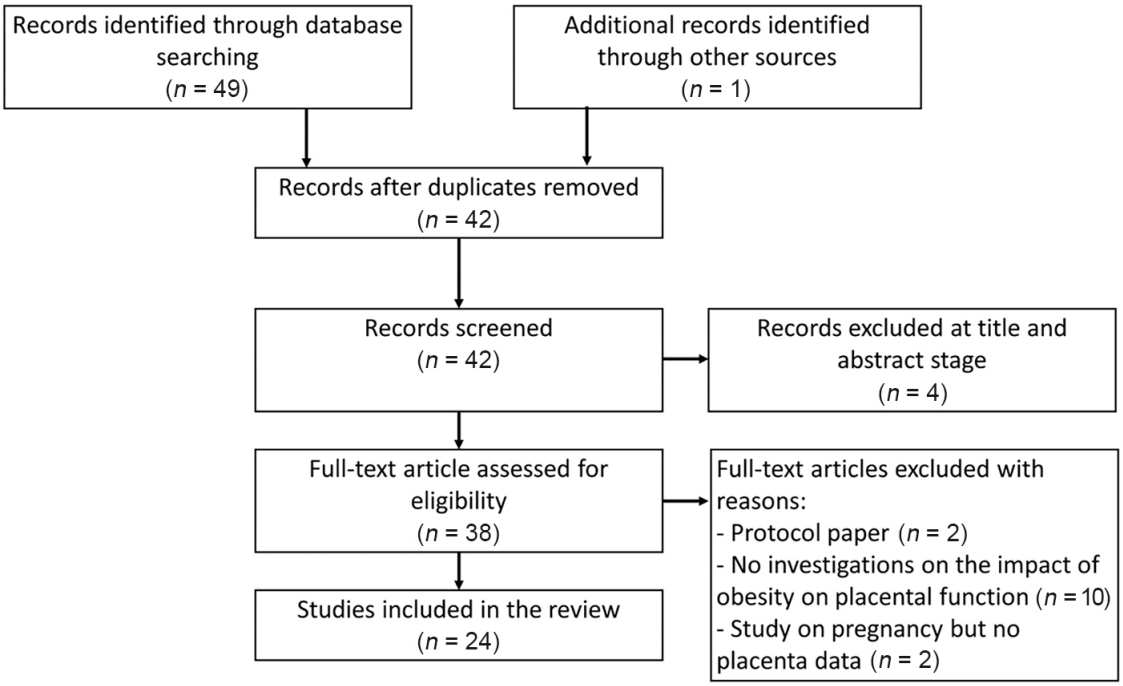

Figure 1. Flow chart of the study selection.

conception obesity sub-section identified 61 downregulated genes associated with inflammation and immune responses, lipid metabolism, cancer pathways, and angiogenesis. The authors concluded that pre-pregnancy obesity alters the placental transcriptome mediated through glucocorticoid receptor signalling pathway and dysregulation of *CCL2, FSTL3, IGFBP1, MMP12, PRG2, PRL, QSOX1, SERPINE2* and *TAC3* genes. These findings were based on the study of 10 placentas and maternal blood samples from 5 obese and 5 non-obese women.

Dysregulated metabolism, inflammation, and endothelial dysfunction

Seven articles were included in the dysregulated metabolism, inflammation, and endothelial dysfunction sub-section. Two of these studies[20,21] were *in vitro* mechanistic studies that found that obesity-related decrease in membrane-metalloendopeptidase (MME, neprilysin) production could lead to dysregulated vasoactive peptides,[20] while lipotoxicity- and TNF-α-induced inflammatory responses in placental syncytiotrophoblast cells may be mediated through activation of JNK/EGR-1 signaling.[21] In another study, there was no evidence to indicate that the effect of lifestyle advice (compared to standard care) was determined by MO.[22] In the other four studies, MO was associated with heightened inflammation (increased TNF-α)[23] and/or oxidative stress,[24] which mediated other deleterious phenotypes including changes in placental morphology, decreased *LEPTIN* gene expression,[23] decreased maternal and neonatal iron status,[25] and impaired endothelial function and risk of preeclampsia indicated by high PAI-1/PAI-2 ratio.[26] The obesity-related inflammation and oxidative stress may be aggravated by other inflammatory disorders such as periodontal disease and GDM.[24]

Placental transport, metabolism and epigenetic ageing

In the placental transport, metabolism and epigenetic ageing sub-section, we included nine studies. We observed that the relationship between MO and placental dysfunction may be genetically modified as MO and genetic ancestry impacted placental epigenetic ageing defined as the difference between 62 CpGs-determined DNA methylation age and gestational age at birth.[18] Obesity-related placental weight increase facilitates glucose delivery to fetuses.[27] The low-grade inflammation and insulin insensitivity in obese-GDM women may be enhanced by increased adipose tissue leptin and chemerin levels.[28] Obesity-related placental leptin signaling may regulate fetal growth.[29] However, markers other than leptin and BMI such as high maternal C-peptide and low insulin sensitivity index (ISHOMA) correlated with decreased serum n-3 polyunsaturated fatty acid (PUFA)[30] required for fetal brain development.[42] Although, BMI was positively associated with C-peptide,[43] the authors were of the opinion that BMI alone may not fully explain the metabolism around the first trimester of pregnancy. Additionally, regardless of BMI status, obese-GDM women experience high cord blood saturated fatty acid (FA) and low PUFA.[31] The low PUFA levels may be due to decreased placental major family domain 2a receptor (MFSD2a) expression. Syncytiotrophoblast synthesis of palmitoleic acid, a FA with anti-inflammatory and insulin-sensitizing properties, is also reduced in obese mothers compared to non-obese controls.[32] A high cord blood alkaline phosphatase (ALP) may be the determinant of FA levels in obese-GDM pregnancies.[31] More so, low

Table 1: Characteristics of included studies

Author, year	Study design	Population/ Sample type	Gestational age at recruitment/Sampling	Treatment/ Intervention	Outcome/Main finding
Pre-pregnancy and peri-conception obesity					
Altmäe *et al.* 2017[19]	Observational case-control study	Pregnant women (n = 10): Pre-pregnancy BMI: ≥ 30.0 kg/m^2 - obese (n = 5) and 18.0–25.0 kg/m^2 - normal weight (n = 5). Placenta Maternal blood	- 24 weeks - 34 weeks - At delivery	NA	61 genes associated with inflammation and immune responses, lipid metabolism, cancer pathways, and angiogenesis were downregulated. The effect of obesity on the placenta is mediated through glucocorticoid receptor signaling pathway and dysregulation of *CCL2, FSTL3, IGFBP1, MMP12, PRG2, PRL, QSOX1, SERPINE2* and *TAC3* genes.
Dysregulated metabolism, inflammation, and endothelial dysfunction					
Musa *et al.* 2023[23]	Observational cohort study	Singleton pregnant women (N = 71): Non-GDM non-obese (n = 14), Non-GDM obese (n = 19), GDM non-obese (n = 15), GDM obese (n = 23). Placenta Maternal and umbilical cord blood	15–37 weeks	NA	MO was associated with diminished *LEPTIN* gene expression, high syncytiotrophoblast TNF-α immunostaining and decreased stromal and fetal vessel IL-6 staining in the placenta in a manner that was partly impacted by GDM status. Both MO and, to a lesser extent, GDM were characterized by specific placental morphometry changes. Obesity and/or GDM also modified maternal blood pressure and weight gain and infant ponderal index.
Weiß *et al.* 2020[20]	*Ex vivo* and *in vitro* mechanistic study	Primary feto-placental endothelial cells (fpEC) isolated from placentas of normal (BMI < 25.0 kg/m^2) and overweight (BMI > 25.0 kg/m^2) women. Cord blood serum	After delivery	Oxygen and TNF-α	Maternal overweight was associated with reduced MME mRNA, protein and release from fpEC. Maternal pre-pregnancy BMI negatively correlated with both cellular and released MME protein. Similarly, maternal pre-pregnancy BMI was negatively associated with cord blood MME. However, hypoxia and TNF-α did not affect MME protein. Maternal BMI-associated decrease in MME protein in fpEC and cord blood may induce an imbalance in vasoactive peptides.
Zambon *et al.* 2018[24]	Observational study	Singleton pregnancies: BMI 18.5–25.0 kg/m^2 (n = 27); BMI ≥ 30.0 kg/m^2 (n = 35), GDM (n = 17)	3rd trimester: saliva and venous plasma; Birth: fetal and placental data	NA	Obesity and periodontitis may act synergistically to enhance inflammatory and oxidative status with increased levels of local and systemic biomarkers (s-TAC, s-CRP, and p-CRP) especially in the presence of GDM.
Moran *et al.* 2017[22]	Multicenter randomized controlled trial	Singletons (n = 1951): overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥ 30.0 kg/m^2)	Maternal venous blood: 14, 28 and 36 weeks Cord blood (n = 1174): after birth and prior to delivery of placenta	Lifestyle advice (n = 989) or Standard care (n = 962)	No evidence to suggest that the effect of the intervention was impacted by maternal BMI category.
Jones *et al.* 2016[25]	Randomized controlled trial	Singletons (maternal blood sample, n = 1613; neonatal cord blood, n = 1573)	Early 2nd trimester about 20 weeks, and 3rd trimester	NA	MO negatively correlated with both maternal and neonatal iron status perhaps mediated through inflammatory pathways
Saben *et al.* 2013[21]	*In vitro* mechanistic study	BeWo cells	NA	Palmitic acid and TNF-α	Lipotoxicity with saturated fatty acid and TNF-α induced inflammation in placental (syncytiotrophoblast) cells by activating JNK/EGR-1 signaling

(continued...)

Author, year	Study design	Population/ Sample type	Gestational age at recruitment/Sampling	Treatment/ Intervention	Outcome/Main finding
Stewart *et al.* 2007[26]	Case-control study	Pregnant women: BMI < 30.0 kg/m^2 (n = 30). BMI ≥ 30.0 kg/m^2 (n = 30). Maternal plasma Non-invasive of skin perfusion	1st, 2nd and 3rd trimester. 4 months postnatal	NA	Obesity is associated with reduced endothelium-dependent and -independent vasodilation. Obesity-associated high PAI-1/ PAI-2 ratio in the first trimester that improved with gestation. Obesity is associated with increased Th2-cytokine that induces chronic preexisting endothelial activation and impaired endothelial function.
Placental transport, metabolism and epigenetic ageing					
Allbrand *et al.* 2022[29]	Observational study	Severely obese singleton pregnancies: 1st trimester BMI ≥ 35.0 kg/m^2 (n =109)/ placental tissues	1st trimester	NA	Fetal growth may be regulated by placental leptin signaling in obese mothers. This is due to the reverse U-shaped relationship observed between placental LEP expression and birth weight z-scores of offsprings as well as sexual dimorphism in LEPRb.
Bandres-Meriz *et al.* 2021[30]	Cross-sectional observational study	Singleton pregnancies (n = 123). Maternal serum	4^{+0}–11^{+6} weeks	NA	First trimester pregnant women with high fasting C-peptide and low IS_{HOMA} (but not BMI or leptin) had decreased serum PUFA. DHA decreased with increased C-peptide only in mothers carrying a female fetus.
Workalemahu *et al.* 2021[18]	Observational multicentre study	Singleton pregnancies (n = 312). Placenta	Within 1 hour after delivery	NA	Maternal cardiometabolic factors and genetic ancestry impact placental epigenetic age acceleration and some of these influences could be male offspring dependent.
Ferchaud-Roucher *et al.* 2019[32]	Observational mechanistic in vitro study	Obese: BMI = 37.5 ± 1.9 kg/m^2, n = 7 and Normal: BMI = 23.6 ± 0.6 kg/m^2, n = 12 mothers. Cytotrophoblasts isolated from placentas.	14–18 weeks After delivery	Uniformly-labelled (U[^{13}C])–Fatty acid mixtures of Palmitic acid, oleic acid, linoleic acid, and docosahexaenoic acid.	MO is associated with decreased syncytiotrophoblast palmitoleic acid synthesis, which may contribute to low-grade inflammation and insulin resistance in the mother, placenta, or fetus (or a combination of the 3).
Prieto-Sánchez *et al.* 2019[31]	Prospective Observational study	Pregnant women: Control (n = 25), Lean-GDM (n = 23), Obese-GDM (n = 20). Placenta, maternal and venous cord blood	- 28–32 weeks - During labour	NA	Placental MFSD2a and cord PUFA are reduced in both lean and obese-GDM pregnancies. Elevated cord blood ALP of obese-GDM mothers could influence the FA levels in these pregnancies.
Tsiotra *et al.* 2018[28]	Observational cohort study	Cesarean section women (n = 38): GDM (n = 15): obese BMI > 30.0 kg/m^2; non-obese BMI < 30.0 kg/m^2. NGT (n = 23): obese and non-obese	Delivery - at the time of Cesarean section	NA	Obese women with GDM had elevated leptin and chemerin and decreased omentin-1 and visfatin compared to obese women with NGT. Increased expression of leptin and chemerin on adipose tissues may promote increased insulin resistance and low-grade inflammation in obese women with GDM.
Guillemette *et al.* 2016[33]	Prospective cohort study	Pregnant women (n = 1034; V1: 1024; V2: 898; V3 [delivery]: 854). Placenta, maternal and cord blood	V1: 5–16 weeks V2: 24–30 weeks V3: Delivery	NA	Decreased maternal adiponectin and vitamin D levels at first trimester is predictive of higher risk of developing GDM. The consequences of maternal dyslipidaemia during gestation on offspring adiposity and metabolic profile was investigated subsequently.

(continued...)

Author, year	Study design	Population/ Sample type	Gestational age at recruitment/Sampling	Treatment/ Intervention	Outcome/Main finding
Acosta *et al.* 2015[27]	Prospective observational cohort study	Pregnant women (n = 52): lean (BMI 18.0–24.9 kg/m^2, n = 20) or overweight/obese (BMI 25.0–54.3 kg/m^2, n = 32). ● Syncytiotrophoblast microvillous and basal plasma membranes from 33 placentas ● Maternal blood = 29 ● Maternal blood and placenta = 10	< 20 weeks	NA	Increased placental weight promotes glucose delivery to the fetuses.
Uhl *et al.* 2015[41]	Observational study	Pregnant women: Controls (lean non-diabetic (BMI 18.0–24.9 kg/m^2, n = 31); Obese non-diabetics (BMI 30.0 kg/m^2, n = 17) and lean diabetics (n = 15). Placental tissues, maternal and cord blood	12–20 weeks	NA	Low dihomo-gamma-linolenic acid and high AA and DHA contents of placental GPL were found in obese women with GDM, with unknown consequences for the fetus. The major component of the supply of AA to fetal circulation was PC, while PE-containing AA was associated with placental and infant growth.
Angiogenic factors					
Beck *et al.* 2022[34]	Multisite prospective observational cohort study	Nulliparous women with a viable singleton pregnancy. First trimester of pregnancy. Maternal blood	Blood samples. 1st trimester (6^{+0} to 13^{+6} weeks of gestation), 2nd trimester (16^{+0} to 22^{+6} weeks of gestation)	NA	High early pregnancy BMI was associated with lower sFlt1 and PlGF concentrations across early pregnancy. Women with class II or III obesity have greater risk of an elevated second-trimester sFlt1/PlGF ratio with associated placental dysfunction.
Heimberger *et al.* 2020[35]	Secondary retrospective analysis of a prospective observational cohort study	Predominantly obese singleton pregnancies with chronic hypertension (n = 115). Maternal blood	22–41 weeks	NA	Elevated sFlt1/PlGF ratio is characterized by an increased risk of maternal adverse outcomes, preeclampsia, preeclampsia with severe features, preterm delivery, low birth weight, neonatal intensive care unit admissions, severe postpartum hypertension and longer hospital stays.
Placental pathology and birth outcomes					
Yang *et al.* 2020[38]	Observational, retrospective study	Pregnant women, singleton deliveries (n = 59,976): Women with VCI (n = 501), Women with normal cord insertion (n = 59,475)	Live birth and stillbirth at 22 weeks	NA	The prevalence of VCI was 0.84%. MO was an independent risk factor for VCI. BMI 30.0–34.9 kg/m^2 (Adj. OR 1.34, P = 0.07) BMI ≥ 35.0 kg/m^2 (Adj. OR 1.84, P = 0.001)
Chen *et al.* 2019[40]	Prospective, observational study	Pre-gravid overweight (BMI ≥ 24.0 kg/m^2) (n = 68) Pre-gravid non-overweight (BMI < 24.0 kg/m^2) (n = 361) Ultrasound scan Maternal blood	First trimester 11–13 weeks GA	NA	Placental vascularization flow index (VFI) was significantly lower in the overweight group (P = 0.037) Placental volume was significantly larger in the overweight group (P = 0.04) Uterine artery pulsatility index was significantly higher in the overweight group (P = 0.021)
Mitanchez *et al.* 2017[37]	Prospective exposure-matched cohort study; Clinical trial NCT02681588	Pregnant women; normal BMI 18.5–24.9 kg/m^2 (n = 222) Obese women BMI ≥ 30.0 kg/m^2 (n = 226). Maternal blood	15–18 weeks GA Preterm births (< 37 weeks) excluded from the analyses	NA	MO was associated with increased skinfold thickness (18.0 mm ± 0.6 mm *vs.* 19.7 mm ± 0.5 mm, P = 0.004); increased serum leptin (11.3 ng/mL *vs.* 15.3 ng/mL, P = 0.02) and; increased placental weight (549 g *vs.* 609 g, P < 0.01) in baby girls but not in boys.

(continued...)

Author, year	Study design	Population/ Sample type	Gestational age at recruitment/Sampling	Treatment/ Intervention	Outcome/Main finding
Berglund *et al.* 2016[36]	Prospective, observational cohort study	Pregnant (singleton) women (n = 331): Overweight = 56; obese = 64; GDM = 79; Healthy normal weight = 132. Maternal blood Placenta Cord blood	24 weeks (n = 269) 34 weeks (n = 310) delivery (n = 310)	NA	Increased placental weight and incidence of macrosomia were higher in the obese women. Apart from glucose, HbA1c, insulin and uric acid, MO was associated with increased CRP, ESR, ferritin and cortisol and decreased transferrin saturation, Hb, vitamin B12 and folate.
Monari *et al.* 2016[39]	Prospective, observational, multicenter study	Women with a history of stillbirth (> 22 weeks). Total of 364 index pregnancies with 320 subsequent pregnancies. Total of 273 babies. 67 (24.5%) babies with an adverse perinatal outcome.	Recruitment (< 12 weeks) Outcome assessment at delivery (including early pregnancy losses, stillbirth, and term delivery)	NA	MO increased from 10.0% to 15.6% compared to the index pregnancy. MO independently predicts an adverse perinatal outcome (Adj OR = 2.1, 95% CI: 1.1–4.3). At univariate analysis, MO was associated with FGR (P = 0.011). At multivariate regression only MO predicted FGR (P = 0.01).

AA: arachidonic acid; ALP: alkaline phosphatase; BMI: body mass index; CCL2: chemokine ligand 2; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DHA: docosahexaenoic acid; EGR-1: early growth response protein-1; FA: fatty acid; FGR: fetal growth restriction; fpEC: primary feto-placental endothelial cells; FSTL3: follistatin-like 3; GA: gestational age; GDM: gestational diabetes mellitus; GPL: glycerophospholipids; Hb: hemoglobin; HbA1c: Glycated hemoglobin; IGFBP1: insulin-like growth factor binding protein 1; IS_{HOMA}: insulin sensitivity index; JNK: c-Jun N-terminal kinase; LEP: leptin; LEPRb: leptin receptor b; MFSD2a: major family domain 2a receptor; MO: maternal obesity; MME: membrane-metalloendopeptidase (neprilysin); MMP12; matrix metallopeptidase 12; N: total population size; n: a sample of the population; NA: not applicable; NGT: normal glucose tolerant; OR: odds ratio; PAI: plasminogen activator inhibitor-1; PC: phosphatidylcholine; p-CRP: plasma C-reactive protein; PE: phosphatidylethanolamine; PlGF: placental growth factor; PRG2; proteoglycan 2: bone marrow; PRL: prolactin; PUFA: polyunsaturated fatty acid; QSOX1: quiescin Q6 sulfhydryl oxidase 1; RCT: randomized control trial; SERPINE2: serpin peptidase inhibitor: clade E: member 2; sFlt1: soluble fms-like tyrosine kinase-1; s-CRP: saliva C-reactive protein; s-TAC: saliva total antioxidant capacity; TAC3: tachykinin 3; Th2: T-helper 2 cells cytokine; TNF-α: Tumor necrosis factor alpha; V: visit; VCI: velamentous cord insertion; BeWo: human placental cell line that originated from a choriocarcinoma and used widely as a cell culture model for the placenta,[44,45] or to simulate *in vivo* syncytialization of placental villous trophoblast.[46]

adiponectin (another insulin-sensitizing adipokine) and vitamin D predicted risk of GDM in the first trimester.[33] Similarly, other adipokines—omentin-1 and visfatin are decreased in obese-GDM women.[28]

Angiogenic factors

In the angiogenic factors sub-section, we included two studies. We observed that adequate placental vascularization is required for a successful pregnancy. MO was reportedly characterized by low placental growth factor (PlGF) and relatively higher levels of its receptor - soluble fms-like tyrosine kinase-1 (sFlt1) represented as high sFlt1/PlGF ratio.[34,35] Consequently, the high sFlt1/PlGF ratio is associated with placental dysfunction,[34] preeclampsia, preterm delivery, low birth weight, need for neonatal intensive care unit admissions, severe postpartum hypertension and longer hospital stays.[35]

Placental pathology and birth outcomes

Lastly, as shown by the five studies included in the placental pathology and birth outcomes sub-section. Obesity and GDM often act synergistically to alter metabolism and inflammatory response with increased C-reactive protein (CRP), cortisol, ferritin, erythrocyte sedimentation rate (ESR), and reduced transferrin saturation, hemoglobin, vitamin B12 and folate.[36] Both are also associated with increased placental weight/volume and macrosomia.[36,37] MO is further associated with increased skin fold thickness, serum leptin in female infants (but not in males),[37] and greater risk of velamentous cord insertion (VCI) that could lead to FGR and prematurity.[38] Nonetheless, MO is an independent risk factor of FGR.[39] Furthermore, being overweight increases the risk of large placental volume and uterine artery pulsatility index but is associated with low vascularization flow index (VFI).[40]

The mechanistic interplay of the key mediators of these obesity-associated placental abnormalities and the consequent adverse pregnancy outcomes are summarised in Figure 2.

DISCUSSION

MO is associated with immediate adverse pregnancy and perinatal outcomes as well as long-term morbidity beyond childhood and adolescence. In fact, studies show that paternal and maternal body composition and diet influence both phenotypic and epigenetic differences up to the second generation.[47,48] This has generated increasing interest in the mechanisms underlying the developmental origins of health and diseases (DoHaD), a concept that attributes chronic diseases in adulthood to nutritional and environmental exposures *in utero*.[49] In this review, we report findings from studies that investigated the impact of MO on placental dysfunction from pre-conception to late gestation and delivery.

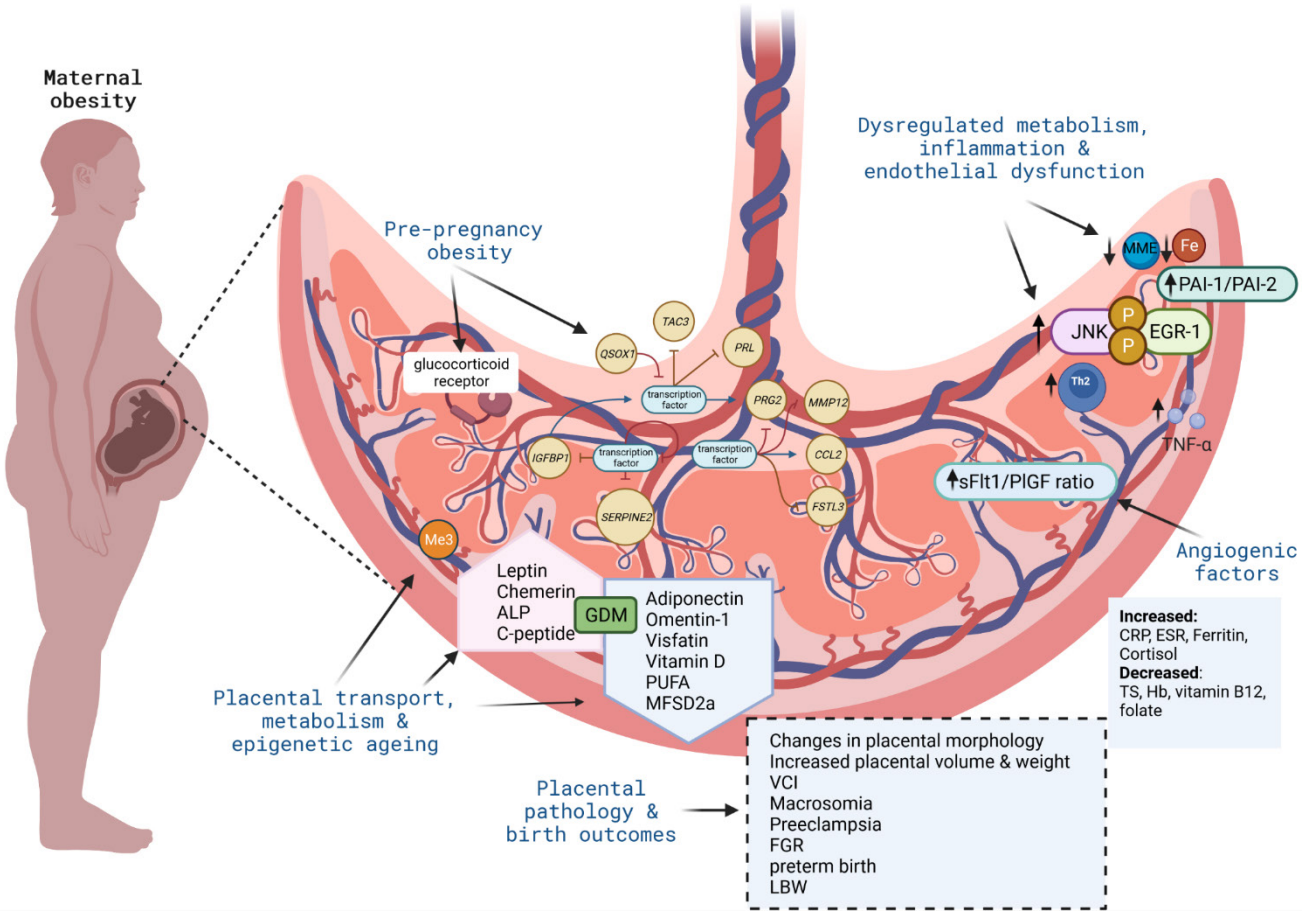

Figure 2. Mechanistic interplay of key mediators of obesity-associated placental dysfunction and adverse pregnancy outcomes. The impact of obesity on placental function begins before conception and mediated through alteration of transcription factors and glucocorticoid receptor signaling. Placental DNA methylation can accelerate placental ageing and predispose to early onset preeclampsia. Maternal obesity also dysregulates adipocytokine secretion, increase ALP and C-peptide and decrease the levels of PUFAs, their transporter (MFSD2a) and vitamin D, which together alter placental transport, metabolism and epigenetic ageing. The risk of poor placental angiogenesis and sub-optimal maternal-fetal transport of nutrients, oxygen, and metabolic byproducts are increased when the sFlt-1/PlGF ratio is high due to increased adiposity. There is also dysregulated metabolism (low iron status), exaggerated pro-inflammatory state (high TNF-α, CRP, Th2-cytokines, ESR, and activation of JNK/EGR-1 signaling), endothelial dysfunction (high PAI-1/PAI-2 ratio), dysregulated vascular tone and vasoactive peptides (low MME) and changes in placental morphology induced by high BMI or lipotoxicity or obesity-related low grade inflammation (increased TNF-α). These abnormalities are worsened by GDM and predispose to several adverse pregnancy outcomes. ALP: alkaline phosphatase; BMI: body mass index; CCL2: chemokine ligand 2; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; EGR-1: early growth response protein-1; FGR: fetal growth restriction; FSTL3: follistatin-like 3; GDM: gestational diabetes mellitus; Hb: hemoglobin; IGFBP1: insulin-like growth factor binding protein 1; JNK: c-Jun N-terminal kinase; LBW: low birth weight; MFSD2a: major family domain 2a receptor; MME: membrane-metalloendopeptidase (neprilysin); MMP12; matrix metallopeptidase 12; PAI: plasminogen activator inhibitor-1; PlGF: placental growth factor; PRG2; proteoglycan 2: bone marrow; PRL: prolactin; PUFA: polyunsaturated fatty acid; QSOX1: quiescin Q6 sulfhydryl oxidase 1; SERPINE2: serpin peptidase inhibitor: clade E: member 2; sFlt1: soluble fms-like tyrosine kinase-1; TAC3: tachykinin 3; TS: transferrin saturation; Th2: T-helper 2 cells cytokine; TNF-α: Tumor necrosis factor alpha; VCI: velamentous cord insertion. Created with BioRender.com

Pre-pregnancy obesity is associated with a higher incidence of co-morbidities including GDM and preeclampsia which contribute to complications in neonates born to obese women. These complications include higher systolic and diastolic blood pressure and altered cardiometabolic profiles in early and late childhood.[50] Longterm prospective studies have also associated pre-pregnancy obesity with a higher BMI in offsprings at all ages and a higher percentage of body fat in these offsprings all the way to adulthood.[51,52] Because the placenta is the medium of transfer of nutrients from the mother to the fetus, there is therefore a need for a better understanding of mechanisms that underlie the association between pre-pregnancy obesity and placental dysfunction.

Data from the studies included in this review show that maternal pre-pregnancy obesity can alter placental transcriptome. Majority of the dysregulated genes include those involved in immune and inflammatory responses, lipid and cholesterol metabolism, cell/tissue growth and regeneration, tissue remodeling, apoptosis, preeclampsia as well as glucocorticoid receptor signaling. One of such genes is *CCL2* which encodes the CCL2 cytokine (monocyte chemoattractant protein 1, MCP-1), an inflammatory chemoattractant.[19] Aberrantly high levels of CCL2 are associated with recurrent pregnancy loss, preeclampsia and preterm birth.[53] *PRG2*, a gene encoding for the proteoglycan 2, pro-eosinophil major basic protein (PRG2) is also dysregulated due to pre-pregnancy obesity.

Increased PRG2 protein is seen in patients with placenta accreta spectrum and placenta previa, both of which are significant causes of pregnancy-associated morbidity.[54] *IGFBP1* is also dysregulated due to pre-pregnancy obesity. Insulin-like growth factors and their binding proteins, the (IGFBPs) are expressed in the placenta and regulate fetal growth. Decreased mRNA and protein expression levels of IGFBP1 have been reported in placentas from LGA deliveries.[55]

The above data demonstrates that there is a linear relationship between pre-pregnancy obesity and poor pregnancy and perinatal outcomes. Additional longitudinal studies incorporating placental investigations will provide further comprehension of the extent to which pre-pregnancy-obesity-associated placental dysfunction is linked to complications in early childhood, adolescence and adulthood. There is also a need for studies assessing the impact of pre-pregnancy weight loss to these outcomes as weight reduction among women with pre-pregnancy obesity before conception is associated with lower newborn body fat content and improved insulin sensitivity during pregnancy.[56]

During pregnancy, the included studies demonstrate that MO is associated with changes in placental morphological parameters including decrease in proportion of stem and terminal villi, increased intervillous space, decreased mature terminal villi, syncytiotrophoblast, fetal capillary and stromal volumes, decrease in maternal blood space and fetal capillary surface areas as well as decreased theoretical diffusion capacity.[23] There is also dysregulated metabolism, inflammatory response and endothelial dysfunction attributed to altered lipid and cholesterol metabolism.[21,57] The placenta is required to maintain high metabolic activity to ensure optimal oxygen, nutrient and ion transport to the developing fetus.[58] In an obesogenic microenvironment, excess nutrients drive increased storage of lipids in the developing placental tissue leading to oxidative stress, inflammation and altered angiogenesis.[57]

Interestingly, animal studies show comparable findings. Pups born to obese female mice were found to be hyperinsulinemic and presented with increased hepatic lipid content and lower concentrations of triglyceride lipase.[59] Pups also presented with similar lipid profiles and insulin resistance in another study with rats.[60] Offspring born to female baboons fed on a high-fat, high-fructose diet were also found to have higher hepatic lipid accumulation and altered transcriptome.[61]

There is also the obesity-associated downregulation of neprilysin (membrane-metalloendopeptidase, MME), in feto-placental endothelial cells before and during pregnancy.[20] MME is expressed on endothelial cells where it plays an important role in the regulation of vascular tone and blood pressure.[62] The downregulation of MME in feto-placental endothelial cells may affect the balance of vasoactive peptides, thus affecting vascular tone regulation. Decreased levels of MME may also contribute to dysregulation of insulin response and insulin resistance. The dysregulated insulin response may be exacerbated by the increased expression of glucose transporters embedded in the plasma membranes of the placental syncytiotrophoblasts such as the non-insulin-dependent glucose transporters (GLUT) isoforms.[63] GLUT1, GLUT4 and GLUT9 were positively correlated with birth weight and fetal growth in pregnancies complicated by obesity and GDM. This is likely due to increased glucose transport across the palcenta and, increased stimulation of the fetal pancreas to release insulin resulting in accelerated fetal growth.[27,64]

Obesity is associated with an upregulation of pro-inflammatory responses.[65,66] Term placentas from obese women show increased accumulation of macrophages and pro-inflammatory mediators.[67] The studies included in this review show that the exaggerated pro-inflammatory state induced by MO could also be mediated by increased CRP,[24] activation of JNK/EGR-1 signaling,[21] and increased release of Th2-cytokines that could alter endothelial function by increasing the PAI-1/PAI-2 ratio and risk of preeclampsia that is characterized by abnormal placentation and extensive endothelial dysfunction.[26] The JNK/EGR-1 signaling pathway,[21] but not MME release,[20] were observed from *in vitro* simulation of the toxic effects of increased maternal adiposity, inflammation and hypoxia on placental development, vascularisation and function.

MO can also disrupt the physiologic ageing of the placenta and impede its hormonal and transport function. MO and genetic ancestry influence placental age acceleration (PAA),[18] that is the difference between placental DNA methylation age and gestational age at birth. MO negatively correlates with PAA,[18] meaning increased adiposity can hinder placental maturity mediated by DNA methylation. DNA methylation-based PAA, which could be male-offspring dependent,[18] may provide insights into clinical predictors of placental ageing. Pregnancy complications such as early onset preeclampsia is associated with higher PAA.[68]

The included studies further showed that obese women exhibit altered angiogenic profiles. Normal placental growth and development requires recruitment of new blood vessels (vasculogenesis and angiogenesis) around the first and second trimesters of pregnancy.[69] Optimal maternal-fetal transport of nutrients, oxygen, and metabolic byproducts is dependent on a closely regulated placental angiogenesis.[70] Placental angiogenesis is regulated amongst others, by PlGF, a proangiogenic member of the vascular endothelial growth factor (VEGF) family, and its receptor sFlt-1.[70,71] PlGF is produced by placental trophoblasts, secreted into maternal circulation along with sFlt-1,[72] and facilitates trophoblast growth and differentiation

during embryogenesis. PlGF is encoded by the *PlGF* gene restricted to human umbilical vein endothelial cells (HUVE) and the placenta.[73] sFlt-1 binds circulating PlGF to inhibit angiogenesis. An elevated sFlt-1/PlGF ratio, that is, low PlGF, indicates angiogenic imbalance, hence abnormal placental development and function later in pregnancy.[71] Inadequate placental vasculature is a common placental pathology resulting in several pregnancy complications.[70] The risk of placental dysfunction and related disorders are increased when the sFlt-1/PlGF ratio is ≥ 38 and > 85 during the second trimester.[74–77] The included studies show that obese women exhibit a high sFlt-1/PlGF ratio at second trimester that is associated with increased risk of placental dysfunction-related disorders including preeclampsia, preterm birth and low birth weight.

The dysfunctional placenta due to obesity-induced placental vascular disorders can lead to other adverse perinatal and neonatal outcomes including risk of velamentous cord insertion,[40] FGR, and stillbirths.[41] There is also evidence of a higher rate of macrosomia[78] accompanied by increased placental weight and volume, increased fetal-placental weight ratios as well as altered placental vascular indices including increased uterine artery pulsatility index and low vascularization flow index.[36,42]

LIMITATIONS

Most of the included studies were observational and showed associations of MO and placental dysfunction but not causality. Though one *in vitro* study[21] demonstrated pro-inflammatory activation of JNK/EGR-1 signaling in syncytiotrophoblast by stimulating placental cells (BeWo) with palmitic acid (lipotoxicity) and TNF-α, the other observed reduced uptake and synthesis of anti-inflammatory and anti-diabetic palmitoleic acid in syncytiotrophoblast of obese mothers.[34] This partly supports the beneficial effect of elevated placental PUFA to maternal metabolism and fetal growth and development. The third *in vitro* study[20] reported exposure of primary feto-placental endothelial cells to hypoxia and TNF-α that can regulate MME expression, did not affect MME production in that experiment. Therefore, more mechanistic studies, systematic reviews and meta-analyses are required to determine whether a causal relationship exist between increased adiposity and any form of placental dysfunction. Futher research should focus on the impact of MO on placental lipid transfer to the fetus. More so, as obesity often co-exist with insulin resistance and high blood pressure, future studies should employ mixed methods of clinical and biochemical investigations across the entire gestational time points. Such studies should account for the role of insulin resistance or hyperglycemia which is a key player in placental function and transfer of nutrients to the fetus.[38] This review is also limited by restrictions imposed on literature search by language and sample size limitations in some of the included studies.

CONCLUSION AND FUTURE PERSPECTIVES

MO is a global epidemic and the findings in this review collectively demonstrate a clear link between MO (including pre-pregnancy and gestational obesity) and placental dysfunction that culminate in adverse antenatal, perinatal and neonatal outcomes. The impact of MO on placental function is not gestation-specific and several parts and/or functions of the placenta can be affected. This deleterious relationship is often exacerbated when GDM co-exist with obesity. The scope of this review was restricted to placental investigations, however, the impact of MO could be far-reaching predisposing the fetus to a higher risk of chronic disease in childhood, adolescence and even through adulthood.[49] Therefore, there is an increased need for a more global understanding of the mechanistic interplay of maternal and fetal factors in obesogenic microenvironments during pregnancy. This will inform the identification of modifiable aspects of pre-pregnancy obesity and excessive gestational weight gain including the critical assessment of timing of weight gain/loss in association with pregnancy and perinatal outcomes. This can ultimately reveal more opportunities to promote health and reduce the risk of MO and related disorders well before conception.

DECLARATIONS

Author contributions

Amabebe E: Conceptualization, Review of articles, Data curation, Writing- Original draft preparation. Ikumi NM: Conceptualization, Review of articles, Data curation, Writing- Original draft preparation. Pillay K: Writing-Reviewing and Editing. Matjila M: Writing—Reviewing and Editing. Anumba DOC: Writing—Reviewing and Editing. All authors have read and approve the final manuscript.

Conflict of interest

The authors declare there are no conflicts of interest.

REFERENCES

1. World Health Organisation. World Health Organisation Fact sheets - Obesity and Overweight. Accessed February 9, 2023. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
2. Onubi OJ, Marais D, Aucott L, Okonofua F, Poobalan AS. Maternal obesity in Africa: a systematic review and meta-analysis. *J Public Health (Oxf)*. 2016;38(3):e218–e231.
3. Brizan JB, Amabebe E. Maternal obesity as a risk factor for Caesarean delivery in sub-Saharan Africa: a systematic review. *Life (Basel)*. 2022;12(6):906.
4. Chopra M, Kaur N, Singh KD, *et al*. Population estimates, consequences, and risk factors of obesity among pregnant and postpartum women in India: results from a national survey and policy recommendations. *Int J Gynaecol Obstet*. 2020;151(Suppl 1):57–67.
5. Shahrir NF, Abdul Jalil R, R Jeganathan JR, *et al*. Maternal obesity and its associated factors and outcomes in klang valley, Malaysia: findings from national obstetric registry. *Malays Fam Physician*. 2021;16(3):56–67.
6. Poston L, Caleyachetty R, Cnattingius S, *et al*. Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet Diabetes*

Endocrinol. 2016;4(12):1025–1036.
7. World Regional Office for Europe. WHO European Regional Obesity Report 2022. Copenhagen: 2022. Accessed February 9, 2023. https://apps.who.int/iris/handle/10665/353747
8. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311(8):806–814.
9. Burton GJ, Fowden AL. The placenta: a multifaceted, transient organ. *Phil Trans R Soc B*. 2015;370(1663):20140066.
10. McAuliffe FM, Killeen SL, Jacob CM, *et al*. Management of prepregnancy, pregnancy, and postpartum obesity from the FIGO Pregnancy and Non-Communicable Diseases Committee: a FIGO (International Federation of Gynecology and Obstetrics) guideline. *Int J Gynecol Obstet*. 2020;151:16–36.
11. Abraham T, Romani AMP. The relationship between obesity and pre-eclampsia: incidental risks and identification of potential biomarkers for pre-eclampsia. *Cells*. 2022;11(9):1548.
12. He XJ, Dai RX, Hu CL. Maternal prepregnancy overweight and obesity and the risk of preeclampsia: a meta-analysis of cohort studies. *Obes Res Clin Pract*. 2020;14(1):27–33.
13. Amabebe E, Anumba DO. Diabetogenically beneficial gut microbiota alterations in third trimester of pregnancy. *Reprod Fertil*. 2021;2(1):R1–R12.
14. Kaul P, Bowker SL, Savu A, Yeung RO, Donovan LE, Ryan EA. Association between maternal diabetes, being large for gestational age and breast-feeding on being overweight or obese in childhood. *Diabetologia*. 2019;62(2):249–258.
15. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. *BMJ*. 2017;356:j1.
16. Dağ ZÖ, Dilbaz B. Impact of obesity on infertility in women. *J Turk Ger Gynecol Assoc*. 2015;16(2):111–117.
17. Gambineri A, Laudisio D, Marocco C, *et al*. Female infertility: which role for obesity? *Int J Obes Suppl*. 2019;9(1):65–72.
18. Workalemahu T, Shrestha D, Tajuddin SM, Tekola-Ayele F. Maternal cardiometabolic factors and genetic ancestry influence epigenetic aging of the placenta. *J Dev Orig Health Dis*. 2021;12(1):34–41.
19. Altmäe S, Segura MT, Esteban FJ, *et al*. Maternal pre-pregnancy obesity is associated with altered placental transcriptome. *PLoS One*. 2017;12(1):e0169223.
20. Weiß E, Berger HM, Brandl WT, *et al*. Maternal overweight downregulates MME (neprilysin) in feto-placental endothelial cells and in cord blood. *Int J Mol Sci*. 2020;21(3):E834.
21. Saben J, Zhong Y, Gomez-Acevedo H, *et al*. Early growth response protein-1 mediates lipotoxicity-associated placental inflammation: role in maternal obesity. *Am J Physiol Endocrinol Metab*. 2013;305(1):E1–E14.
22. Moran LJ, Fraser LM, Sundernathan T, *et al*. The effect of an antenatal lifestyle intervention in overweight and obese women on circulating cardiometabolic and inflammatory biomarkers: secondary analyses from the LIMIT randomised trial. *BMC Med*. 2017;15(1):32.
23. Musa E, Salazar-Petres E, Arowolo A, Levitt N, Matjila M, Sferruzzi-Perri AN. Obesity and gestational diabetes independently and collectively induce specific effects on placental structure, inflammation and endocrine function in a cohort of South African women. *J Physiol*. 2023;601(7):1287–1306.
24. Zambon M, Mandò C, Lissoni A, *et al*. Inflammatory and oxidative responses in pregnancies with obesity and periodontal disease. *Reprod Sci*. 2018;25(10):1474–1484.
25. Jones AD, Zhao G, Jiang YP, *et al*. Maternal obesity during pregnancy is negatively associated with maternal and neonatal iron status. *Eur J Clin Nutr*. 2016;70(8):918–924.
26. Stewart FM, Freeman DJ, Ramsay JE, Greer IA, Caslake M, Ferrell WR. Longitudinal assessment of maternal endothelial function and markers of inflammation and placental function throughout pregnancy in lean and obese mothers. *J Clin Endocrinol Metab*. 2007;92(3):969–975.
27. Acosta O, Ramirez VI, Lager S, *et al*. Increased glucose and placental GLUT-1 in large infants of obese nondiabetic mothers. *Am J Obstet Gynecol*. 2015;212(2):227.e1–227.e7.
28. Tsiotra PC, Halvatsiotis P, Patsouras K, *et al*. Circulating adipokines and mRNA expression in adipose tissue and the placenta in women with gestational diabetes mellitus. *Peptides*. 2018;101:157–166.
29. Allbrand M, Eklund D, Cao Y, Nilsson K, Lodefalk M. Gene expression of leptin, leptin receptor isoforms and inflammatory cytokines in placentas of obese women - Associations to birth weight and fetal sex. *Placenta*. 2022;117:64–71.
30. Bandres-Meriz J, Majali-Martinez A, Hoch D, *et al*. Maternal C-peptide and insulin sensitivity, but not BMI, associate with fatty acids in the first trimester of pregnancy. *Int J Mol Sci*. 2021;22(19):10422.
31. Prieto-Sánchez MT, Blanco-Carnero JE, Ruiz-Palacios M, Pagán A, Ruiz-Alcaraz AJ, Larqué E. Increased alkaline phosphatase in cord blood of obese diabetic mothers is associated to polyunstaurated fatty acid levels. *Ann Nutr Metab*. 2019;75(3):153–162.
32. Ferchaud-Roucher V, Barner K, Jansson T, Powell TL. Maternal obesity results in decreased syncytiotrophoblast synthesis of palmitoleic acid, a fatty acid with anti-inflammatory and insulin-sensitizing properties. *FASEB J*. 2019;33(5):6643–6654.
33. Guillemette L, Allard C, Lacroix M, *et al*. Genetics of Glucose regulation in Gestation and Growth (Gen3G):a prospective prebirth cohort of mother-child pairs in Sherbrooke, Canada. *BMJ Open*. 2016;6(2):e010031.
34. Beck C, Allshouse A, Silver RM, *et al*. High early pregnancy body mass index is associated with alterations in first- and second-trimester angiogenic biomarkers. *Am J Obstet Gynecol MFM*. 2022;4(3):100614.
35. Heimberger S, Mueller A, Ratnaparkhi R, Perdigao JL, Rana S. Angiogenic factor abnormalities and risk of peripartum complications and prematurity among urban predominantly obese parturients with chronic hypertension. *Pregnancy Hypertens*. 2020;20:124–130.
36. Berglund SK, García-Valdés L, Torres-Espinola FJ, *et al*. Maternal, fetal and perinatal alterations associated with obesity, overweight and gestational diabetes: an observational cohort study (PREOBE). *BMC Public Health*. 2016;16:207.
37. Mitanchez D, Jacqueminet S, Nizard J, *et al*. Effect of maternal obesity on birthweight and neonatal fat mass: a prospective clinical trial. *PLoS One*. 2017;12(7):e0181307.
38. Yang M, Zheng Y, Li M, *et al*. Clinical features of velamentous umbilical cord insertion and Vasa previa: a retrospective analysis based on 501 cases. *Medicine (Baltimore)*. 2020;99(51):e23166.
39. Monari F, Pedrielli G, Vergani P, *et al*. Adverse perinatal outcome in subsequent pregnancy after stillbirth by placental vascular disorders. *PLoS One*. 2016;11(5):e0155761.
40. Chen CY, Chang HT, Chen CP, Sun FJ. First trimester placental vascular indices and volume by three-dimensional ultrasound in pre-gravid overweight women. *Placenta*. 2019;80:12–17.
41. Uhl O, Demmelmair H, Segura MT, *et al*. Effects of obesity and gestational diabetes mellitus on placental phospholipids. *Diabetes Res Clin Pract*. 2015;109(2):364–371.
42. Zou R, El Marroun H, Voortman T, Hillegers M, White T, Tiemeier H. Maternal polyunsaturated fatty acids during pregnancy and offspring brain development in childhood. *Am J Clin Nutr*. 2021;114(1):124–133.
43. Bandres-Meriz J, Dieberger AM, Hoch D, *et al*. Maternal obesity affects the glucose-insulin axis during the first trimester of human pregnancy. *Front Endocrinol (Lausanne)*. 2020;11:566673.
44. Pattillo RA, Gey GO. The establishment of a cell line of human hormone-synthesizing trophoblastic cells in vitro. *Cancer Res*. 1968;28(7):1231–1236.
45. Heaton SJ, Eady JJ, Parker ML, *et al*. The use of BeWo cells as an *in vitro* model for placental iron transport. *Am J Physiol Cell Physiol*. 2008;295(5):C1445–C1453.
46. Orendi K, Gauster M, Moser G, Meiri H, Huppertz B. The choriocarcinoma cell line BeWo: syncytial fusion and expression of syncytium-specific proteins. *Reproduction*. 2010;140(5):759–766.
47. Sanchez-Garrido MA, Ruiz-Pino F, Velasco I, *et al*. Intergenerational influence of paternal obesity on metabolic and reproductive health parameters of the offspring: male-preferential impact and involvement of Kiss1-mediated pathways. *Endocrinology*. 2018;159(2):1005–1018.
48. Cropley JE, Eaton SA, Aiken A, *et al*. Male-lineage transmission of an acquired metabolic phenotype induced by grand-paternal obesity. *Mol*

Metab. 2016;5(8):699–708.
49. Hoffman DJ, Powell TL, Barrett ES, Hardy DB. Developmental origins of metabolic diseases. *Physiol Rev*. 2021;101(3):739–795.
50. Gaillard R, Welten M, Oddy WH, *et al*. Associations of maternal prepregnancy body mass index and gestational weight gain with cardio-metabolic risk factors in adolescent offspring: a prospective cohort study. *BJOG*. 2016;123(2):207–216.
51. Laitinen J, Power C, Järvelin MR. Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. *Am J Clin Nutr*. 2001;74(3):287–294.
52. Tequeanes ALL, Gigante DP, Assunção MCF, Chica DAG, Horta BL. Maternal anthropometry is associated with the body mass index and waist: height ratio of offspring at 23 years of age. *J Nutr*. 2009;139(4):750–754.
53. Lin Z, Shi JL, Chen M, Zheng ZM, Li MQ, Shao J. CCL2:an important cytokine in normal and pathological pregnancies: a review. *Front Immunol*. 2022;13:1053457.
54. Zhang ET, Hannibal RL, Badillo Rivera KM, *et al*. PRG2 and AQPEP are misexpressed in fetal membranes in placenta previa and percreta. *Biol Reprod*. 2021;105(1):244–257.
55. Nawathe AR, Christian M, Kim SH, Johnson M, Savvidou MD, Terzidou V. Insulin-like growth factor axis in pregnancies affected by fetal growth disorders. *Clin Epigenetics*. 2016;8:11.
56. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. *BMJ*. 2017;356:j1.
57. Saben J, Lindsey F, Zhong Y, *et al*. Maternal obesity is associated with a lipotoxic placental environment. *Placenta*. 2014;35(3):171–177.
58. Vaughan O, Fowden A. Placental metabolism: substrate requirements and the response to stress. *Reprod Domest Animals*. 2016;51:25–35.
59. Alfaradhi MZ, Fernandez-Twinn DS, Martin-Gronert MS, Musial B, Fowden A, Ozanne SE. Oxidative stress and altered lipid homeostasis in the programming of offspring fatty liver by maternal obesity. *Am J Physiol Regul Integr Comp Physiol*. 2014;307(1):R26–R34.
60. Lomas-Soria C, Reyes-Castro LA, Rodríguez-González GL, *et al*. Maternal obesity has sex-dependent effects on insulin, glucose and lipid metabolism and the liver transcriptome in young adult rat offspring. *J Physiol*. 2018;596(19):4611–4628.
61. Puppala S, Li C, Glenn JP, *et al*. Primate fetal hepatic responses to maternal obesity: epigenetic signalling pathways and lipid accumulation. *J Physiol*. 2018;596(23):5823–5837.
62. Turner AJ, Elwyn Isaac R, Coates D. The neprilysin (NEP) family of zinc metalloendopeptidases: Genomics and function. *BioEssays*. 2001;23(3):261–269.
63. Stanirowski PJ, Szukiewicz D, Pyzlak M, Abdalla N, Sawicki W, Cendrowski K. Impact of pre-gestational and gestational diabetes mellitus on the expression of glucose transporters GLUT-1, GLUT-4 and GLUT-9 in human term placenta. *Endocrine*. 2017;55(3):799–808.
64. Stanirowski PJ, Szukiewicz D, Pyzlak M, Abdalla N, Sawicki W, Cendrowski K. Analysis of correlations between the placental expression of glucose transporters GLUT-1, GLUT-4 and GLUT-9 and selected maternal and fetal parameters in pregnancies complicated by diabetes mellitus. *J Matern Fetal Neonatal Med*. 2019;32(4):650–659.
65. Ramsay JE, Ferrell WR, Crawford L, Wallace AM, Greer IA, Sattar N. Maternal obesity is associated with dysregulation of metabolic, vascular, and inflammatory pathways. *J Clin Endocrinol Metab*. 2002;87(9):4231–4237.
66. Denison FC, Roberts KA, Barr SM, Norman JE. Obesity, pregnancy, inflammation, and vascular function. *Reproduction*. 2010;140(3):373–385.
67. Challier JC, Basu S, Bintein T, *et al*. Obesity in pregnancy stimulates macrophage accumulation and inflammation in the placenta. *Placenta*. 2008;29(3):274–281.
68. Mayne BT, Leemaqz SY, Smith AK, Breen J, Roberts CT, Bianco-Miotto T. Accelerated placental aging in early onset preeclampsia pregnancies identified by DNA methylation. *Epigenomics*. 2017;9(3):279–289.
69. Chen DB, Zheng J. Regulation of placental angiogenesis. *Microcirculation*. 2014;21(1):15–25.
70. Reynolds LP, Caton JS, Redmer DA, *et al*. Evidence for altered placental blood flow and vascularity in compromised pregnancies. *J Physiol*. 2006;572(1):51–58.
71. Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. *J Hum Hypertens*. 2017;31(12):782–786.
72. Lecarpentier É, Vieillefosse S, Haddad B, *et al*. Placental growth factor (PlGF) and sFlt-1 during pregnancy: physiology, assay and interest in preeclampsia. *Ann Biol Clin (Paris)*. 2016;74(3):259–267.
73. Hauser S, Weich HA. A heparin-binding form of placenta growth factor (PlGF-2) is expressed in human umbilical vein endothelial cells and in placenta. *Growth Factors*. 1993;9(4):259–268.
74. Herraiz I, Simón E, Gómez-Arriaga PI, *et al*. Angiogenesis-related biomarkers (sFlt-1/PLGF) in the prediction and diagnosis of placental dysfunction: an approach for clinical integration. *Int J Mol Sci*. 2015;16(8):19009–19026.
75. Stepan H, Herraiz I, Schlembach D, *et al*. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. *Ultrasound Obstet Gynecol*. 2015;45(3):241–246.
76. Zeisler H, Llurba E, Chantraine F, *et al*. Predictive value of the sFlt-1:PlGF ratio in women with suspected preeclampsia. *N Engl J Med*. 2016;374(1):13–22.
77. Rana S, Powe CE, Salahuddin S, *et al*. Angiogenic factors and the risk of adverse outcomes in women with suspected preeclampsia. *Circulation*. 2012;125(7):911–919.
78. Harmon KA, Gerard L, Jensen DR, *et al*. Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. *Diabetes Care*. 2011;34(10):2198–2204.