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

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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/m², 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.[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] The prevalence of MO is over 20.0% in Europe,[6] 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
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. 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.

MO is a well-established risk factor for poor placental function as well as obstetric and birth complications. These include preeclampsia, fetal growth restriction (FGR), preterm birth (PTB), and caesarean delivery. 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. MO and associated inflammation and insulin resistance can, therefore, lead to gestational diabetes mellitus (GDM) and consequently placental dysfunction. Obese mothers with GDM are three times more likely to have large for gestational age (LGA) or macrosomic deliveries. The downstream effect particularly for LGA or macrosomic babies is an increased likelihood to develop childhood obesity and metabolic disease later in life.

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.

A successful pregnancy is dependent on a balanced interaction between maternal cardiometabolic functioning, genetic predisposition and optimal placental development and function. 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-conception 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 included in the pre-pregnancy and peri-
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,\[25\] decreased maternal and neonatal iron status,\[25\] and impaired endothelial function and risk of preeclampsia indicated by high PAI-1/PAI-2 ratio.\[25\] 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.\[26\] 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)\[34\] 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
Observational MO was associated with 61 genes associated with dysregulated metabolism, inflammation, and endothelial dysfunction. MO negatively correlated with Randomized Obesity and periodontitis may be impacted by maternal BMI 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.

**Table 1: Characteristics of included studies**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design</th>
<th>Population/ Sample type</th>
<th>Gestational age at recruitment/Sampling</th>
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<td>Pre-pregnancy and peri-conception obesity</td>
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<tr>
<td>Altmäe et al. 2017[28]</td>
<td>Observational case-control study</td>
<td>Pregnant women (n = 10); Pre-pregnancy BMI ≥ 30.0 kg/m² - obese (n = 5) and 18.0–25.0 kg/m² - normal weight (n = 5). Placenta Maternal blood</td>
<td>- 24 weeks - 34 weeks - At delivery</td>
<td>NA</td>
<td>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, FSTL1, LIG3, MMP2, PRG2, PHL, G0N1, SERPINE2 and TAC1 genes.</td>
</tr>
<tr>
<td>Musa et al. 2023[29]</td>
<td>Observational cohort study</td>
<td>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</td>
<td>15–37 weeks</td>
<td>NA</td>
<td>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.</td>
</tr>
<tr>
<td>Weiss et al. 2020[31]</td>
<td>Ex vivo and in vitro mechanistic study</td>
<td>Primary feto-placental endothelial cells (fpEC) isolated from placentas of normal (BMI &lt; 25.0 kg/m²) and overweight (BMI &gt; 25.0 kg/m²) women. Cord blood serum</td>
<td>After delivery</td>
<td>Oxygen and TNF-α</td>
<td>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.</td>
</tr>
<tr>
<td>Zambon et al. 2018[26]</td>
<td>Observational study</td>
<td>Singleton pregnancies: BMI 18.5–25.0 kg/m² (n = 27); BMI ≥ 30.0 kg/m² (n = 38), GDM (n = 17)</td>
<td>3rd trimester: saliva and venous plasma; Birth: fetal and placental data</td>
<td>NA</td>
<td>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.</td>
</tr>
<tr>
<td>Moran et al. 2017[27]</td>
<td>Multicenter randomized controlled trial</td>
<td>Singletontons (n = 1951): overweight BMI 25.0–29.0 kg/m² and obese BMI ≥ 30.0 kg/m²</td>
<td>Maternal venous blood: 14, 28 and 36 weeks Cord blood (n = 1174): after birth and prior to delivery of placenta</td>
<td>Lifestyle advice (n = 909) or Standard care (n = 962)</td>
<td>No evidence to suggest that the effect of the intervention was impacted by maternal BMI category.</td>
</tr>
<tr>
<td>Jones et al. 2016[30]</td>
<td>Randomized controlled trial</td>
<td>Singletontons (maternal blood sample, n = 1613; neonatal cord blood, n = 1575)</td>
<td>Early 2nd trimester about 20 weeks, and 3rd trimester</td>
<td>NA</td>
<td>MO negatively correlated with both maternal and neonatal iron status perhaps mediated through inflammatory pathways.</td>
</tr>
<tr>
<td>Saben et al. 2013[31]</td>
<td>In vitro mechanistic study</td>
<td>BeWo cells</td>
<td>NA</td>
<td>Palmitic acid and TNF-α</td>
<td>Lipotoxicity with saturated fatty acid and TNF-α induced inflammation in placental (syncytiotrophoblast) cells by activating JNK/EGR-1 signaling.</td>
</tr>
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**Notes:**
- BMI: Body Mass Index
- GDM: Gestational Diabetes Mellitus
- MME: Maternal Matrix Metalloproteinase 9
- TNF-α: Tumor Necrosis Factor-alpha
- LEPTIN: Leptin
- TAC: Tumor Necrosis Factor-alpha}

**References:**
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- [2]:
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**Additional Notes:**
- Pre-pregnancy and peri-conception obesity
  - Altmäe et al. 2017: Observational case-control study
  - Population: Pregnant women (n = 10); Pre-pregnancy BMI ≥ 30.0 kg/m² - obese (n = 5) and 18.0–25.0 kg/m² - normal weight (n = 5). Placenta Maternal blood
  - Gestational age: - 24 weeks - 34 weeks - At delivery
  - Treatment: NA
  - Outcome: 61 genes associated with dysregulated metabolism, inflammation, and endothelial dysfunction. MO negatively correlated with Randomized Obesity and periodontitis may be impacted by maternal BMI 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.

- Dysregulated metabolism, inflammation, and endothelial dysfunction
  - Musa et al. 2023: Observational cohort study
  - Population: 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
  - Gestational age: 15–37 weeks
  - Treatment: NA
  - Outcome: 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: Ex vivo and in vitro mechanistic study
  - Population: Primary feto-placental endothelial cells (fpEC) isolated from placentas of normal (BMI < 25.0 kg/m²) and overweight (BMI > 25.0 kg/m²) women. Cord blood serum
  - Treatment: Oxygen and TNF-α
  - Outcome: 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: Observational study
  - Population: Singleton pregnancies: BMI 18.5–25.0 kg/m² (n = 27); BMI ≥ 30.0 kg/m² (n = 38), GDM (n = 17)
  - Treatment: Lifestyle advice (n = 909) or Standard care (n = 962)
  - Outcome: 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: Multicenter randomized controlled trial
  - Population: Singletontons (n = 1951): overweight BMI 25.0–29.0 kg/m² and obese BMI ≥ 30.0 kg/m²
  - Treatment: No evidence to suggest that the effect of the intervention was impacted by maternal BMI category.

- Jones et al. 2016: Randomized controlled trial
  - Population: Singletontons (maternal blood sample, n = 1613; neonatal cord blood, n = 1575)
  - Treatment: NA
  - Outcome: MO negatively correlated with both maternal and neonatal iron status perhaps mediated through inflammatory pathways.

- Saben et al. 2013: In vitro mechanistic study
  - Population: BeWo cells
  - Treatment: Palmitic acid and TNF-α
  - Outcome: Lipotoxicity with saturated fatty acid and TNF-α induced inflammation in placental (syncytiotrophoblast) cells by activating JNK/EGR-1 signaling.
Amabebe et al.: Maternal obesity-related placental dysfunction

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<th>Outcome/Main finding</th>
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<tbody>
<tr>
<td>Stewart et al. 2007[20]</td>
<td>Case-control study</td>
<td>Pregnant women; BMI &lt; 30.0 kg/m² (n = 30); BMI ≥ 30.0 kg/m² (n = 30); Maternal plasma Non-invasive of skin perfusion</td>
<td>1st, 2nd and 3rd trimester. 4 months postnatal</td>
<td>NA</td>
<td>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.</td>
</tr>
<tr>
<td>Allbrand et al. 2022[21]</td>
<td>Observational study</td>
<td>Severely obese singleton pregnancies: 1st trimester BMI ≥ 35.0 kg/m² (n = 109)/ placental tissues</td>
<td>1st trimester</td>
<td>NA</td>
<td>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 offspring as well as sexual dimorphism in LEP Rh</td>
</tr>
<tr>
<td>Bandres-Meriz et al. 2021[22]</td>
<td>Cross-sectional observational study</td>
<td>Singleton pregnancies (n = 123); Maternal serum</td>
<td>4th–11th weeks</td>
<td>NA</td>
<td>First trimester pregnant women with high fasting C-peptide and low IS (but not BMI or leptin) had decreased serum PUFA. DHA decreased with increased C-peptide only in mothers carrying a female fetus.</td>
</tr>
<tr>
<td>Workalemahu et al. 2021[23]</td>
<td>Observational multicentre study</td>
<td>Singleton pregnancies (n = 312); Placenta</td>
<td>Within 1 hour after delivery</td>
<td>NA</td>
<td>Maternal cardiometabolic factors and genetic ancestry impact placental epigenetic age acceleration and some of these influences could be male offspring dependent.</td>
</tr>
<tr>
<td>Ferchaud-Roucher et al. 2019[24]</td>
<td>Observational mechanistic in vitro study</td>
<td>Obese: BMI ≥ 37.5 ± 1.9 kg/m², n = 7 and Normal: BMI ≥ 23.6 ± 0.6 kg/m², n = 12 mothers. Cytotrophoblasts isolated from placentas.</td>
<td>14–18 weeks</td>
<td>Uniformly-labelled (U[13C])–Fatty acid mixtures of Palmitic acid, oleic acid, linoleic acid, and docosahexaenoic acid.</td>
<td>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).</td>
</tr>
<tr>
<td>Prieto-Sánchez et al. 2019[25]</td>
<td>Prospective Observational study</td>
<td>Pregnant women: Control (n = 25), Lean GDM (n = 23), Obese GDM (n = 20); Placenta, maternal and venous cord blood</td>
<td>- 28–32 weeks - During labour</td>
<td>NA</td>
<td>Placental MISD2a 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.</td>
</tr>
<tr>
<td>Tsiotra et al. 2018[26]</td>
<td>Observational cohort study</td>
<td>Cesarean section women (n = 38); GDM (n = 15); obese BMI &gt; 30.0 kg/m²; non-obese BMI &lt; 30.0 kg/m²; NGT (n = 23): obese and non-obese</td>
<td>Delivery - at the time of Cesarean section</td>
<td>NA</td>
<td>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.</td>
</tr>
<tr>
<td>Guillemette et al. 2016[27]</td>
<td>Prospective cohort study</td>
<td>Pregnant women (n = 1034; V1: 1024; V2: 898; V3 [delivery]: 854); Placenta, maternal and cord blood</td>
<td>V1: 5–16 weeks V2: 24–30 weeks V3: Delivery</td>
<td>NA</td>
<td>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.</td>
</tr>
</tbody>
</table>
**Prospective placental vascularization flow**

The prevalence of VCI was 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[25]  Multi-site prospective observational cohort study  Nulliparous women with a viable singleton pregnancy. First trimester of pregnancy. Maternal blood  Blood samples, 1st trimester (6+ to 13+6 weeks of gestation), 2nd trimester (16+3 to 22+9 weeks of gestation)  NA  High early pregnancy BMI was associated with lower sFlt1 and PI GF concentrations across early pregnancy. Women with class II or III obesity have a greater risk of an elevated second-trimester sFlt1/PIGF ratio with associated placental dysfunction.

Heimberger et al. 2020[26]  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/PIGF 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[27]  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/m² (Adj. OR 1.34, P = 0.07) BMI ≥ 35.0 kg/m² (Adj. OR 1.84, P = 0.001)

Chen et al. 2019[28]  Prospective, observational study  Pre-gravid overweight (BMI ≥ 24.0 kg/m²) (n = 68) Pre-gravid non-overweight (BMI < 24.0 kg/m²) (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)

Mitanechez et al. 2017[29]  Prospective exposure-matched cohort study; Clinical trial NCT02681588  Pregnant women; normal BMI 18.5–24.9 kg/m² (n = 222) Obese women BMI ≥ 30.0 kg/m² (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 < 0.001) in baby girls but not in boys.
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 (PIGF) and relatively higher levels of its receptor—soluble fms-like tyrosine kinase-1 (sFlt1) represented as high sFlt1/PIGF ratio.[34,35] Consequently, the high sFlt1/PIGF 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 (VFII).[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.
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. 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. 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. Aberrantly high levels of CCL2 are associated with recurrent pregnancy loss, preeclampsia and preterm birth. 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. 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.

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.

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. There is also dysregulated metabolism, inflammatory response and endothelial dysfunction attributed to altered lipid and cholesterol metabolism. The placenta is required to maintain high metabolic activity to ensure optimal oxygen, nutrient and ion transport to the developing fetus. In an obesogenic microenvironment, excess nutrients drive increased storage of lipids in the developing placental tissue leading to oxidative stress, inflammation and altered angiogenesis. 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. Pups also presented with similar lipid profiles and insulin resistance in another study with rats. 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.

There is also the obesity-associated downregulation of nephrilysin (membrane-metalloendopeptidase, MME), in feto-placental endothelial cells before and during pregnancy. MME is expressed on endothelial cells where it plays an important role in the regulation of vascular tone and blood pressure. 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. 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 placenta and, increased stimulation of the fetal pancreas to release insulin resulting in accelerated fetal growth.

Obesity is associated with an upregulation of pro-inflammatory responses. Term placentas from obese women show increased accumulation of macrophages and pro-inflammatory mediators. The studies included in this review show that the exaggerated pro-inflammatory state induced by MO could also be mediated by increased CRP, a proangiogenic member of the vascular endothelial growth factor (VEGF) family, and its receptor sFlt-1, which provides insights into clinical predictors of 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), which is the difference between placental DNA methylation age and gestational age at birth. MO negatively correlates with PAA, meaning increased adiposity can hinder placental maturity mediated by DNA methylation. DNA methylation-based PAA, which could be male-offspring dependent, may provide insights into clinical predictors of placental ageing. Pregnancy complications such as early onset preeclampsia is associated with higher PAA.

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. Optimal maternal-fetal transport of nutrients, oxygen, and metabolic byproducts is dependent on a closely regulated placental angiogenesis. Placental angiogenesis is regulated amongst others, by PIGF, a proangiogenic member of the vascular endothelial growth factor (VEGF) family, and its receptor sFlt-1. PIGF is produced by placental trophoblasts, secreted into maternal circulation along with sFlt-1, and facilitates trophoblast growth and differentiation.
during embryogenesis. PI GF is encoded by the PI GF gene restricted to human umbilical vein endothelial cells (HUVE) and the placenta.\(^{[73]}\) sFlt-1 binds circulating PI GF to inhibit angiogenesis. An elevated sFlt-1/PI GF ratio, that is, low PI GF, indicates angiogenic imbalance, hence abnormal placental development and function later in pregnancy.\(^{[74]}\) Inadequate placental vasculature is a common placental pathology resulting in several pregnancy complications.\(^{[75]}\) The risk of placental dysfunction and related disorders are increased when the sFlt-1/PI GF ratio is ≥ 38 and > 85 during the second trimester.\(^{[76–77]}\) The included studies show that obese women exhibit a high sFlt-1/PI GF 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,\(^{[48]}\) FGR, and stillbirths.\(^{[49]}\) There is also evidence of a higher rate of macrosomia\(^{[70]}\) 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.\(^{[16,42]}\)

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\(^{[28]}\) 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. Further 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. Pilay 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.

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Amabebe et al.: Maternal obesity-related placental dysfunction


