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Article type : Review Article

Review shows that maternal obesity induces serious adverse neonatal effects and is associated with childhood obesity in their offspring

Running title: Maternal obesity and neonatal and childhood outcomes

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.14269

Abbreviations

BMI: body mass index

OR: odd ratio

CI: confidence interval

GD: gestational diabetes

LGA: large for gestational age

Abstract

Aim

Obesity at the start of pregnancy has been rising worldwide, increasing the risk of maternal complications. We reviewed the independent effects of maternal obesity during pregnancy on neonatal adverse outcomes and the risk of childhood obesity and adverse cardio-metabolic profiles.

Methods

We searched MEDLINE for papers published in English between December 2007 and November 2017, focusing primarily on human studies published in the last five years. However, we also chose to highlight examples derived from model animals that could bring mechanistic insight and preventive and therapeutic avenues.

Results

Our review showed that maternal obesity had independent effects on neonatal adverse outcomes such as macrosomia, perinatal mortality and birth defects. Maternal obesity alone increased the risks for adverse neonatal outcomes, including macrosomia, perinatal

mortality, induced preterm birth and birth defects. In association with excess gestational weight gain, mainly early in pregnancy, increased the risks of childhood obesity, higher fat mass and, to a smaller extent, adverse cardio-metabolic profiles. Animal models highlighted sexually dimorphic responses to maternal obesity.

Conclusion

Maternal obesity induced serious adverse neonatal effects and was associated with childhood obesity in their offspring. The peri-conceptional period is critical for metabolic programming and obese women need close monitoring from conception.

Key words:

Child obesity, gestational diabetes, gestational weight gain, metabolic programming, neonatal outcomes

Key notes:

- This study reviewed the independent effects of maternal obesity during pregnancy on neonatal adverse outcomes and the risk of childhood obesity and adverse cardio-metabolic profiles.
- We found that maternal obesity had serious adverse neonatal effects, such as macrosomia, perinatal mortality and birth defects, and was associated with childhood obesity in their offspring.
- The peri-conceptional period is critical for metabolic programming and obese women need close monitoring from conception.

INTRODUCTION

The incidence of obesity during pregnancy has been rising worldwide, in parallel with the global increase in obesity in the general population. In most developing countries, the prevalence of overweight, defined as a body mass index (BMI) of at least 25 kg/m^2, in women aged 20-49 years residing in both urban and rural areas is higher than that of underweight women, with a BMI of less than18.5 kg/m^2. The median ratio of overweight to underweight is 5.8:1 and of 2.1:1 in urban and rural areas, respectively (1). In the United States, in 2009, more than one in five pregnant women was obese, with a BMI of at least 30 kg/m^2, across almost every age and racial ethnic group (2). In European countries, the prevalence of maternal obesity has been reported to be 7-25% and it seems to be strongly related to social and educational inequalities (3). As a consequence, maternal obesity has become a major public health concern because of the increased risks for adverse outcomes for both the mother and child. Indeed, maternal obesity has been associated with multiple adverse outcomes, including preeclampsia, altered fetal growth, neonatal morbidity and childhood obesity. Despite the fact that obesity is often accompanied by co-morbidities such as gestational diabetes (GD), these have not always been controlled for the studies that have been carried out. Therefore, the main aim of the this review was to examine the comorbidities associated with maternal gestational obesity and systematically review the neonatal adverse outcomes and the risk of obesity and cardio-metabolic risks in childhood associated with maternal obesity and associated comorbidities *per se* during pregnancy. We also decided to provide selected information from animal models to provide an insight into the putative mechanisms and potential prevention strategies that could be used in humans.

METHODS

The MEDLINE database was systematically reviewed for papers on human subjects published in English between December 2007 and November 2017, with a particular focus on studies published in the last past years of the study period. We used the search terms maternal obesity, pre-eclampsia, diabetes mellitus, gestational weight gain, infant, newborn, "mortality, macrosomia, birth weight, preterm, congenital anomalies, population attributable risk, childhood, childhood obesity and adiposity and childhood outcomes. The review did not exclude commonly referenced and highly regarded older publications. We also included relevant references from the reference lists of the papers identified by our search strategy. We gave priority to meta-analyses and systematic reviews, randomised control trials and large cohort and case-control studies that were judged relevant. Finally, in order to limit the number of references to the journal's requirements, if several references indicated the same results, we only cited the most recent in the last five years of the study period.

The results are organised in the first section, which focuses on maternal comorbidities, and the second section, which is dedicated to neonatal and childhood outcomes. In the following text, unless stated otherwise, overweight refers to a BMI of more than 25 and less than 30 obesity to a BMI of at least 30 and severe obesity to a BMI of at least 35. Infant death is defined as mortality between birth and one year of age and large for gestational age (LGA) is a birth weight above the 90th percentile for gestational age. Odds ratios (OR) and Z-scores are presented as the mean value followed by the 95% confidence interval (95% CI) when available.

In the second part of this paper, the aim was not to perform a systematic review, but to highlight significant concepts and treatment or preventive avenues to be tested in humans, as a starting point for further human studies and preventive strategies.

Maternal conditions associated with obesity and adverse outcomes

Maternal obesity is associated with a significant increase in maternal morbidities during pregnancy and some of these, such as GD and hypertension, alter fetal health and are independently associated with adverse neonatal outcomes.

Preeclampsia

Pre-eclampsia is defined as the occurrence of *de novo* hypertension with blood pressure >140/90mmHg and proteinuria ≥0.3g/24 hours after 20 weeks of gestation. There is a clear relationship between increasing BMI and the risk of preeclampsia. A meta-analysis of 29 prospective cohort studies demonstrated a risk ratio for preeclampsia of 2.68 (95% CI 2.40-3.00), for obese women and 3.43 (95% CI 2.59-4.55) for women with severe obesity. That study concluded that maternal adiposity was an independent risk factor for pre-eclampsia in both nulliparous and multiparous women (4). Another systematic review reported that obese women were 3-10 times more likely to have pre-eclampsia, but that the exact biological causal pathway remained poorly defined (5). To date, the specific effect of preeclampsia on the fetus and neonate in an obese pregnancy has not been addressed.

Diabetes

The association between maternal obesity and GD has been reported by many studies. A systematic review of observational studies published between 1977 and 2007 found an OR of 3.01 (95% CI 2.34-3.87) for obese women and 5.55 (4.27-7.21) for severely obese women, when compared to women of normal weight (6). In a multi-ethnic population where the prevalence of maternal obesity was 14%, the population attributable risk fraction indicated that one-third of the diabetes cases could have been avoided if all the obese women had a normal BMI (7).

Therefore, obesity and diabetes are linked. Indeed, the maternal metabolic environment in obese women is characterised by a greater insulin resistance at the beginning of pregnancy compared to normal weight women. Cytokines produced by the adipose tissue affect post receptor insulin signalling, thus enhancing insulin resistance during pregnancy and leading to maternal hyperinsulinaemia, hyperglycaemia and GD. Nevertheless, a report based on data from the Hyperglycemia and Adverse Pregnancy Outcome study showed that maternal GD and obesity were independently associated with adverse pregnancy outcomes and that the combination of the two had a greater impact than either one alone (8).

Another important point is that diabetes may also precede pregnancy, as growing numbers of pregnant women are affected by type 2 diabetes, diagnosed either before or during pregnancy. In an Australian cohort of 138 pregnancies with type 2 diabetes, 80% of the women who were affected were overweight or obese (9).

Once diagnosed, diabetes is treated and glycaemic control levels are targeted. In obese women with GD, achieving the targeted levels of glycaemic control has only been associated with better outcomes in women treated with insulin. In one study, the obese women who achieved their targeted levels of glycaemia just by dieting had a two to three times higher risk of adverse pregnancy outcomes than normal weight women with well controlled GD (10).

Gestational weight gain

The Institute of Medicine recommends that gestational weight gain is limited to 5-9 kg for obese women. Despite this, 47–72% of obese women gain more weight than recommended and excessive gestational weight gain in obese pregnancies is associated with higher birth weight (11) and an increased risk of preterm birth (12).

A meta-analysis that aimed to evaluate the effects of interventions based on diet and physical activity, showed that these interventions reduced gestational weight gain compared to controls by a mean of -0.70kg (95% CI -0.92 to -0.48kg). Interventions do not significantly reduce offspring complications, irrespective of maternal BMI, although those that are mainly based on physical activity have been shown to reduce the odds for GD (13). Finally, although dietary and physical activity counselling at the pre-conceptional stage has been shown to result in a reduction in gestational weight gain, there was no effect on gestational week of delivery nor on infant birth weight in overweight, obese and severely obese women (14).

Bariatric surgery is increasingly used as an effective treatment for obesity and reduces weight before pregnancy and gestational weight gain. One study showed that women who had undergone bariatric surgery had lower risks of preeclampsia, GD and macrosomia, but the risk of small neonates and preterm birth was increased (15).

Maternal obesity and perinatal outcomes

The perinatal outcomes following maternal obesity are schematically represented in Figure 1.

Maternal obesity and fetal growth

The relationship between maternal obesity and high birth weight is well documented. Indeed, several meta-analyses have demonstrated that maternal obesity was associated with excessive fetal growth, with an average increased risk of 2.5 to three-fold (16-19) (Table 1). Nevertheless, it seems that gestational weight gain above the recommended limits contributes more to LGA births than being obese, with population attributable fractions of 15.9% and 8.9%, respectively (20).

Data concerning the association between maternal obesity and low birth weight are controversial, with both reports of decreased and moderately increased risk (Table 1) (16, 19, 21).

Foetal and neonatal mortality

Maternal overweight and obesity are the highest ranking modifiable risk factors for stillbirth in high-income countries, with a population attributable fraction of 8-18%, contributing to around 8,000 stillbirths at 22 weeks of gestation or more per year. The population attributable fraction for pre-existing diabetes in high-income countries is 3.3-4.7%, contributing to around 2,200 stillbirths per year (22).

Even a modest increase in maternal BMI has been associated with increased risks of fetal, perinatal, neonatal or infant deaths. One meta-analysis showed that the relative risk for each five-unit unit increase in maternal BMI was 1.21 (95% CI 1.09-1.35) for fetal death, 1.24 (95% CI 1.18-1.30) for stillbirth, 1.16 (95% CI 1.00-1.35) for perinatal death, 1.15 (95% CI 1.07-1.23) for neonatal death and 1.18 (95% CI 1.09-1.28) for infant death (23).

Most studies did not consider whether GD or other maternal or fetal complications were present in their analysis of mortality rates. In a large cohort study that excluded pregnancies with malformations and pre-gestational diabetes, maternal obesity was associated with increased risks of fetal and infant death with ORs of 2.32 (95%1.64-3.28) and 1.97 (1.13-3.45), respectively. Moreover, for each one-point increase in maternal BMI over 23 kg/m^2, the risk increased by 7% fetal death and 6% for infant death (24). The results were the same when the women with hypertension were excluded.

The mechanisms behind this excess mortality were not identified. Maternal obesity, however, was shown to be associated with neonatal complications, such as post-term birth, that increase the risks of fetal and perinatal death. One meta-analysis showed a linear association between the risk of birth after 41 weeks of gestation and maternal BMI: the OR for each five-unit increase in BMI was 1.13 (95% CI 1.05-1.21) (25).

Prematurity

The risk of preterm birth before 37 weeks was not, or just slightly, increased by maternal obesity, with a population attributable fraction for high BMI of less than 5% (20). In contrast, the risk of preterm birth before 33-32 weeks was significantly increased (Table 2). Nevertheless, the latter risk concerned induced preterm, but not spontaneous, preterm birth (21,26). This could be expected, as obese women are more likely to develop preeclampsia and GD, which often lead to elective preterm delivery.

Birth defects

The increased risk of fetal malformations in obese pregnant women has been reviewed in detail. Studies showed that obesity doubled the risk of neural tube defects, especially spina bifida, increased the risk of cardiovascular malformations and limb abnormalities by 30%, the risk of a cleft lip and, or, palate by 20% and anorectal atresia and hydrocephalus by 50-70% (27,28). Maternal obesity has also been associated with about a two-fold increased risk of omphalocele and diaphragmatic hernia (29). Conversely, the risk of laparoschisis is significantly decreased in obese women, probably because of the influence of maternal age, as the prevalence of obesity increases with age, whereas laparoschisis affects younger women.

Most of these malformations have also been described in cases of pre-GD, which raises the issue of abnormal maternal glycaemic balance at the beginning of pregnancy, and in cases of undiagnosed type 2 diabetes. Nevertheless, when cases with pre-GD are excluded, the risk of cardiac malformations or neural tube defects are only slightly changed (28). Although omphalocele and diaphragmatic hernia are not usually reported in cases of maternal diabetes, associations between malformations and maternal obesity teratogenicity factors directly associated with maternal obesity deserve to be studied further.

Other adverse neonatal outcomes

A reduced Apgar score of less than seven at five minutes has been associated with maternal obesity with an OR of 1.40 (95% CI 1.27-1.54), but neonatal cord pH has not (30). In a large cohort study that included 1,423,929 term neonates from obese or normal-weight mothers, the adjusted hazard ratios for cerebral palsy were 1.28 (95% CI 1.11-1.47) for a maternal BMI of 30 to 34.9, 1.54 (95% CI 1.24-1.93) for 35 to 39.9 and 2.02 (95% CI 1.46-2.79) for BMI over 40. An estimated 45% of the association between maternal BMI and rates of cerebral palsy in full-term children was reported to be mediated through asphyxia-related neonatal morbidity (31).

One study reported that when mothers were obese, their infants had a significantly higher risk of being admitted to the neonatal intensive care unit, with an OR of 1.91 (95% CI 1.60-2.29) (16). Moreover, another study found a significant relationship between maternal obesity and respiratory distress (OR 1.71, 95% CI 1.38-2.11), resuscitation (OR 1.75, 95% CI 1.26-2.43) and increased tube feeding requirements (OR 1.51, 1.08-2.10) (19).

A large cohort study showed that, compared to neonates born to women who were normal weight, those born to women with a BMI of more than 40 had an increased risk of a birth injury to the peripheral nervous system and to the skeleton, with ORs of 3.80 (95% CI 12.83-5.12) and 2.59 (95% CI 2.10-3.21), respectively, and an increased risk of hypoglycaemia of 3.48 (95% CI 3.20-3.78) (32). The latter may have been related to maternal diabetes, which is frequently associated with obesity, as the adjustment for maternal blood glucose levels performed in another study eliminated this relationship (33).

Effect of maternal obesity on health of offspring during childhood

The concept of the early origins of adult disease was first developed by David Barker in the late 1980s. He observed that cardiovascular risk, as well as the risk of diabetes and metabolic syndrome in adulthood, was increased in low birth weight individuals. This resulted in his hypothesis that restricted *in utero* nutrition permanently alters tissue structures and functions, and hence metabolism, increasing the risk of cardiovascular and metabolic disorders in adulthood (34). Since then extensive reviews have shown that maternal obesity during pregnancy has also been shown to contribute to the developmental origins of health and disease (35).

The following text explores the relative contribution of maternal pre-pregnancy BMI, gestational weight gain and diabetes, to body composition and cardio-metabolic disorders of children born to obese mothers.

Childhood obesity

When women are overweight before pregnancy this doubles the risk of their offspring being overweight or obese and obese mothers treble the risk of offspring overweight or obesity (18). Excessive gestational weight gain has also been associated with an increased risk of offspring obesity of up to 40% (36). The highest risk was observed during childhood (OR 1.91, 95% CI 121-3.02) with a subsequent decrease (OR 1.32, 95% CI 1.14-1.53) from five to 17 years of age (36).

Many studies built on population-based prospective cohorts in different populations, from early pregnancy or birth, have reported that offspring adiposity was positively associated with maternal BMI and gestational weight gain (Table 3) (37-47).

Nevertheless, the timing of any gestational weight gain during pregnancy is important. Several studies showed that high early pregnancy weight gain was associated with high BMI and adiposity in offspring during childhood. Indeed, any weight gain in the first 14 weeks of gestation has been shown to be incrementally associated with increased offspring adiposity,

whereas between 14 and 36 weeks, only a gestational weight gain of more than 500g per week has been associated with increased offspring adiposity (47). In line with these findings, the Generation R study found that weight gain in early pregnancy was associated with childhood BMI and adiposity, independent of maternal pre-pregnancy BMI and later pregnancy weight gain (45).

Childhood cardio-metabolic profile

Adverse cardio-metabolic profiles that have been associated with maternal obesity or excessive gestational weight gain include increased blood pressure, impaired lipid profile, insulin resistance or elevated inflammatory markers (40,42-45,47). However, these associations have not been shown to be very strong and they may have been mainly mediated by offspring adiposity. In the Generation R study, the clustering of cardio-metabolic risk factors was three-fold higher in the offspring of obese mothers, compared to children from normal weight mothers, and 1.7-fold higher in offspring from women who gained excess weight in early pregnancy (45).

Effect of maternal obesity and maternal diabetes or macrosomia on child health

One meta-analysis found a significantly increased Z-score of 0.28 (956% CI 0,09-0,47) when there was maternal diabetes, but this is no longer apparent after the data were adjusted for maternal BMI (48). These results provide support for the suggestion that GD cannot be evaluated as an independent risk factor for childhood overweight or obesity without accounting for potential confounding maternal obesity. Furthermore, it is important to consider the timing of the mother's exposure to diabetes during pregnancy. It is possible that pre-existing type 2 diabetes at the beginning of a pregnancy does not have the same impact as GD.

Macrosomia has also been shown to increase the risk of obesity, type 2 diabetes and metabolic syndrome in offspring. One study reported a two-fold increase in the risk of obesity in offspring when the birth weight was more than 4kg (49). The prevalence of metabolic syndrome in children between the ages of 6-11 was 50% in those born LGA to diabetic mothers, 21% in those born to diabetic mothers with normal birth weights and 29% in those born LGA born to non-diabetic mothers. In that study, a regression analysis demonstrated that LGA status and maternal obesity each increased the risk of metabolic syndrome by approximately two-fold, while maternal diabetes was not independently significant (50). These results mean that children who are LGA at birth and exposed to an intrauterine environment of either diabetes or maternal obesity face an increased risk of developing metabolic syndrome. Moreover, maternal obesity on its own, exclusive of a GD diagnosis, may affect offspring outcome regardless of birth weight.

What can we learn from animal models?

As stated above, prospective cohort studies have highlighted associations between maternal obesity and gestational weight gain and the risk of obesity or adverse metabolic profile in childhood. However, they have not supported conclusions about causality. Indeed, other factors involved in offspring health, such as maternal smoking or vitamin D deficiency, have been associated with childhood obesity. These factors have often been observed during obese pregnancies, but have mostly been overlooked (39). Moreover, many postnatal expositions, in particular breastfeeding duration and the age when solid food is introduced, have been shown to influence the risk of higher childhood adiposity (51).

Due to the experimental control of developmental conditions, and the short life cycle of many animals, animal models have been widely studied to try and decipher mechanisms linking maternal and offspring obesity. Nevertheless, extreme diets, such as those with 60% fat in mice, are usually needed to induce maternal obesity in rodents, as model animals will often

adjust their feed intake to maintain their body condition. Moreover, it is critical to understand the physiological similarities and differences between humans and animal models, including non-rodent animals, in order to infer significant information from studies generated in animals (52). Since considerable data are available on animal models, the aim of the following section is to shed light on key observations and treatment opportunities suggested by studies using animal models, without attempting to exhaustively review the literature.

Effects of maternal obesity and diabetes during gestation in animal models

In contrast to what is commonly expected, excess maternal nutrition or maternal obesity in animals has usually been shown to lead to fetal growth restriction rather than excess fetal growth, as a result of impaired placental function (53). However, macrosomia and, or, increased neonatal BMI has been observed in offspring born to obese sheep (54) and non-human primates (55). Nevertheless, feeding an obesogenic diet to females before and during pregnancy generally increased the incidence of obesity and insulin resistance in offspring (56,57). It is important to note that GD does not occur spontaneously in most animals, although increased insulin resistance is a common feature during pregnancy. Thus, GD may be induced through pharmaceutical intervention, with the use of streptozotocin or alloxan to destroy maternal pancreatic beta-cells before pregnancy or genetic modification or maternal infusion with glucose at specific stages of pregnancy. A review on maternal obesity reported that macrosomia was not a consistent finding in offspring born to diabetic dams, but impaired glucose homeostasis and beta cell dysfunction were reported in the offspring (52).

Key observations

The key observations in animal models include sexual dimorphism in feto-placental responses and long-term offspring outcomes in response to maternal obesity (58). The placenta, of fetal origin, is the active maternal-fetal interface and a key actor in programming through its nutrient sensing, nutrient transfer and endocrine function (59). The sexually dimorphic gene expression responses demonstrated in the mouse placenta, in response to

the maternal diet (60), have now been confirmed in other species, together with physiological observations (58). It is interesting to observe that relatively few of the above cited studies in humans considered fetal or child sex and omitting this factor may wipe out important observations. Indeed, we showed in a prospective human cohort study that neonatal fat mass and cord serum leptin concentrations were increased in girls born to obese women compared to normal weight women, but not in boys (61).

Many studies in animals demonstrate the importance of the pre-conceptional and peri-conceptional periods in the programming of offspring health (62,63). In particular, maternal obesity has been associated with distinct gene expression profiles in the uterus of obese female rats, affecting inflammatory and lipid metabolism pathways and associated with lipid accumulation (64). Gene expression in early and late pre-implantation embryo development has also been shown to be affected by maternal obesity and a high fat diet in both rats and rabbits (64). Moreover, embryo transfer experiments in mice have shown that pre-gestational and peri-conceptional maternal obesity independently affect offspring development (65), thus highlighting the importance of these periods when considering potential corrective interventions.

Treatment or prophylactic opportunities

Although preconceptional obesity directly affects offspring development, weight loss before pregnancy has been shown to prevent obesity-induced transcriptional changes in the placenta, although the offspring phenotype was still affected by previous maternal obesity (66).

Modifications in dietary macro-nutriments and micro-nutriments to modify placental function and possibly modulate fetal growth and metabolism have been explored. Since high-fat and obesogenic diets have been shown to alter epigenetic marks in the fetus and placenta (67), maternal intake of methyl donors such as folic acid and methionine could modify the

methylation of fetal metastable epialleles, as demonstrated in both mice and humans (68, 69).

Maternal obesity affects placental vascularisation and function. Thus, maternal supplementation with amino-acids, such as citrulline or arginine, that improve placental function through multiple mechanisms, could be used for maternal treatment. Indeed, one study reported that citrulline supplements improved placental function in rats and enhanced fetal growth (70), whereas arginine supplements improved insulin sensitivity in dams fed a high-fat diet (71). Preliminary clinical data has already indicated that arginine supplements may also be beneficial for obese pregnant women (72).

Maternal obesity is also clearly accompanied by systemic inflammation. One study showed that increasing the n-3/n-6 polyunsaturated fatty acid ratio in the maternal plasma of obese mice reduced maternal inflammation and prevented adverse offspring metabolic outcomes (73).

Finally, very encouraging results have been obtained using maternal exercise before and, or, during pregnancy in obese female rats and improving offspring outcomes until old age in male offspring (74). Exercise strategies have been attempted in obese women, but compliance may be an issue.

CONCLUSION

There is no doubt that maternal obesity during pregnancy induces short-term effects on the fetus and the neonate, but it also affects health during childhood, independently of other maternal comorbidities (Figure 1). The effects on fetal growth, birth defects and the incidence of perinatal death have been particularly striking. There is also growing evidence, not detailed here, that maternal obesity has an impact on the long-term metabolic and cardiovascular health of their offspring, as well as their mental health, through direct effects

of nutrition on epigenetic mechanisms (75). Prevention strategies are urgently needed and the data shown here indicate that improving physical activity in obese women is beneficial and that bariatric interventions prior to pregnancy must also be considered. Data obtained by animal and human studies also call for the management of obese women, starting from the peri-conceptional period or even before. Moreover, work on animals and work on humans indicate that different effects could be expected between boys and girls. These observations, if confirmed in humans, could lead to the development of specific maternal nutritional strategies that depend on the sex of their fetus. Finally animal data suggest that further studies on targeted nutritional interventions in obese pregnancies must be performed.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Figure 1: Summary of the major findings from epidemiological studies on the effect of maternal obesity on pregnancy, fetal development, neonatal outcomes and childhood health.

Interestingly, when it was adjusted for maternal BMI, gestational diabetes had no effect on childhood obesity. In contrast, the combination of maternal obesity and excess maternal weight gain or excess fetal growth increased the risks of childhood obesity and metabolic syndrome, respectively. OR: Odd Ratio

Table 1: Association of maternal obesity with high or low birth weight reported from meta-analysis.

High birth weight		**Odds ratio**	**95% confidence interval**
Liu et al, 2016 (16)	BW > 4kg	2.92	2.67-3.20
	BW > 90th percentile	1.88	1.67-2.11
Gaudet et al, 2014 (17)	BW > 4.5kg	2.77	2.22-3.45
	BW > 4kg	2.17	1.92-2.45
	BW > 90th percentile	2.42	2.16-2.72
Yu et al, 2013 (18)	BW > 4.5kg	3.23	2.39-4.37
	BW > 4kg	2.00	1.84-2.18
	BW > 90th percentile	2.08	1.95-2.23
Heslehurst et al, 2008 (19)	High birth weight	2.36	2.29-2.42
Low birth weight			
Liu et al, 2016 (16)	BW < 2kg	1.24	1.09-1.41
McDonald et al, 2010 (21)	BW < 2.5kg	0.84	0.75-0.95
Heslehurst et al, 2008 (19)	Low birth weight	0.84	0.78-0.90

BW, birth weight.

Table 2: Association of maternal obesity with preterm birth reported from meta-analyses.

Preterm birth < 37 weeks		**Odds ratio**	**95% confidence interval**
Liu et al, 2016 (16)		1.05	1.05-1.09
McDonald et al, 2010 (21)	All	1.10	0.99-1.21
	Induced preterm birth	1.56	1.42-1.71
	Spontaneous preterm birth	0.88	0.74-1.04
Torloni et al, 2009 (26)	All	0.89	0.78-1.01
	Induced preterm birth	1.48	1.33-1.65
Heslehurst et al, 2008 (19)		1.23	1.15-1.30
Preterm birth < 33 weeks			
McDonald et al, 2010 (21)		1.45	1.21-1.71
Preterm birth < 32 weeks			
Torloni et al, 2009 (26)	All	1.48	1.20-1.81
	Induced preterm birth	2.00	1.47-2.73
Heslehurst et al, 2008 (19)	All morbidly obese	1.59	1.47-1.71

Table 3: Association of obesity or adiposity in childhood with maternal obesity and excessive gestational weight gain reported from prospective cohorts.

	Country	Sample n /mean age at investigation	Risk associated with maternal obesity	Risk associated with excessive gestational weight gain (GWG)
Sorensen et al, 2016 (37)	Denmark	30566 / 7 years	OR = 2.34, 95% CI 2.05-2.68	
Hivert et al, 2016 (38)	Massachusetts	989 / 7.7 years		First trimester: OR = 1.31, 95% CI 1.10-1.55
Robinson et al, 2015 (39)	United Kingdom	991 / 6 years	β = 0.70, 95% CI 0.50-0.90	β = 0.32, 95% CI 0.18, 0.47
Daraki et al, 2015 (40)	Greece	618 / 4 years	OR = 1.83, 95% CI 1.18-2.81	
Castillo et al, 2015 (41)	Brazil	3156 / 6 years	+1 kg/m^2 in maternal BMI: +0.18% body fat %	+1kg in GWG: +0.18% body fat %
Kaar et al, 2014 (42)	Colorado	313 / 10.4 years	Each +1 kg/m^2 in maternal BMI*: β = 0.13, 95% CI 0.02-0.25	Each +1kg/m^2 in maternal BMI*: β = 0.34, 95% CI 0.25-0.44
Oostvogels et al, 2014 (43)	Netherlands	3321 / 5.7 years	Waist-height-ratio: β = 0.199, 95% CI 0.097–0.300	
Gaillard et al, 2014 (44)	Netherlands	4871 / 6 years	OR = 3.84, 95% CI 3.01-4.90	

Gaillard et al, 2015 (45)	Netherlands	5908 / 6 years	GWG in early pregnancy: OR = 1.19, 95% CI 1.10-1.29
Crozier et al, 2010 (46)	United Kingdom	948 / 6 years	Excess GWG according to IOM: β = 0.30, 95% CI 0.11-0.49
Frazer et al, 2010 (47)	United Kingdom	5154 / 9 years	> 500g/weeks, < 14 weeks¶: +0.624, 95% CI: 0.241-1.007 > 500g/week, 14-36 weeks¶: +0.623, 95% CI: 0.257-0.989

IOM: Institute of Medicine, OR: odd ratio, CI: confidence interval, β: regression coefficient

*Association with maternal pre-pregnancy BMI when gestational weight gain was adequate or excessive, according to the Institute of Medicine recommendations.

¶Mean difference (95% confidence interval) in offspring BMI per 1-kg change in maternal pre-pregnancy weight and 400g/week gestational weight gain.

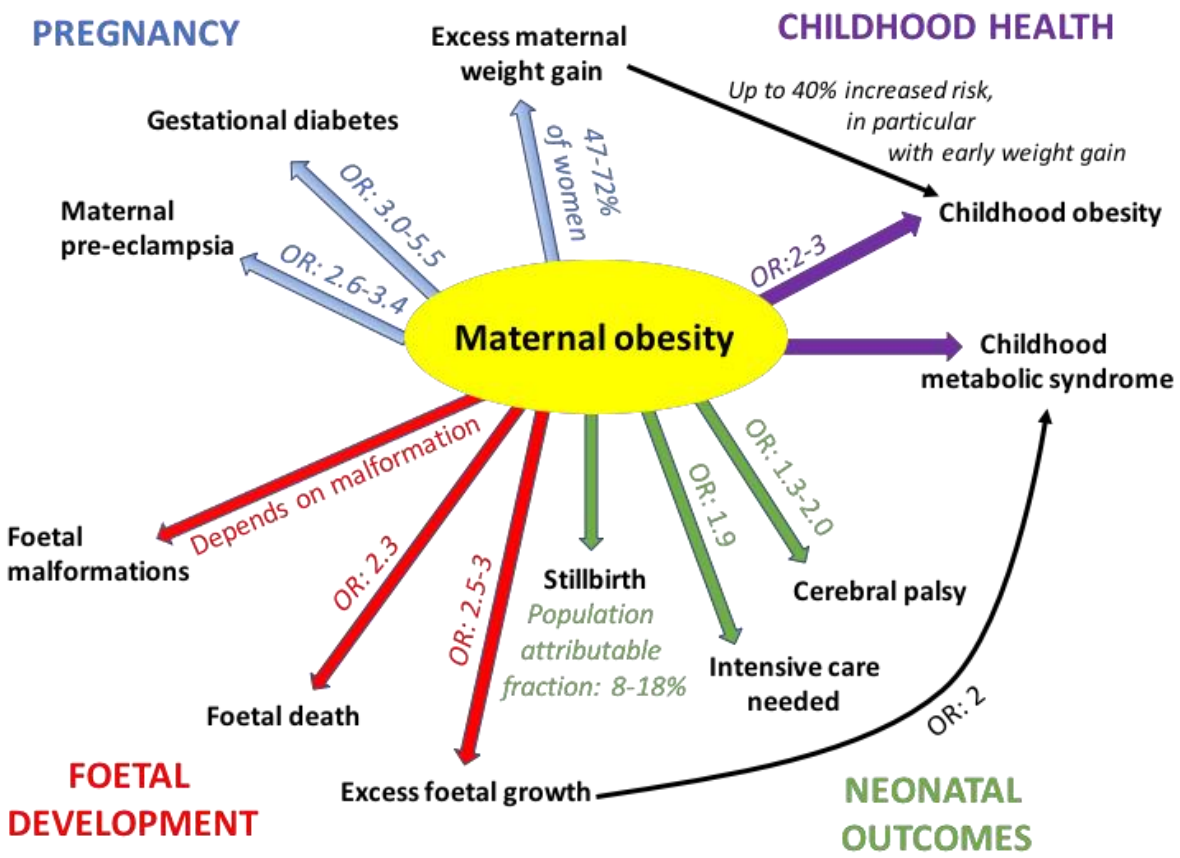

Figure 1