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Review Article

Pre-pregnancy obesity: Maternal, neonatal and childhood outcomes

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Abstract. Nowadays, obesity rates have an increasing tendency, since the incidence of obesity in both developed and developing countries is still rising over the years. Maternal pre-pregnancy obesity seems to have an influence on both obstetrical and neonatal outcomes. Many researchers have focused on pregnancies of obese nulliparous, non diabetic women as well as on the medical profile of their neonates, with conflicting conclusions. Additionally, several studies have followed these neonates through their childhood and adult life in order to observe them for any occurrence towards specific diseases. In our study, literature was reviewed and results are presented, into two groups. The first group summarizes the correlation of high maternal prepregnancy Body Mass Index (BMI) with the rates of hypertensive disorders, fertility, cesarean section and maternal mortality, while the second group correlates maternal BMI to neonatal Apgar score, neonatal admission to NICU, preterm delivery, congenital defects, birthweight, and weight status after birth, child morbidity, respiratory problems as asthma and children's mortality. Maternal pre-pregnancy obesity tends to have an important negative impact on the above mentioned outcomes. However, further research, in certain fields, needs to be carried out in order to gain a clear image.

Keywords: Body mass index, BMI, pregnancy, complications

1. Introduction

Over recent years, obesity has been one of the most important health problems, while obesity-related health problems come first among the most common causes of death worldwide. According to World Health Organization (WHO) [1], obese adults reached 300 million worldwide. It is estimated that within next decades, obesity will be the most serious single cause of death surpassing smoking [1, 2].

This increase in prevalence of obesity also seems to have an influence on pregnant women since more and more get incorporated into obese groups. According to recent studies, it is estimated that, in USA, one third of pregnant women are obese [3], while rates of maternal obesity, at delivery, are 36.2% higher than in 1991 [4]. Moreover, during the decade 1993–2003, obesity in pregnancy increased up to 43% in nine states in USA [5].

Another point of interest is, that the incidence of obesity among children increases with an alarming rate and according to WHO, in 2010 almost 43 million children under 5 years old, around the world, were

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overweight. By investigating the causes of this fact and in an effort to explain it, many studies have shown that there are critical periods affecting the occurrence of obesity in later adult life. These crucial periods are considered to be prenatal period, years between 5–7 old and puberty [6].

It is well known that obesity has severe consequences on the person's health since it seems that it is correlated with diabetes mellitus type 2, hypertension, insulin resistance, dislipidemia, coronary heart disease, venous thrombosis, stroke, osteoarthritis, respiratory disorders, obstructive sleep apnea syndrome, endocrinological disorders, kidney disease, cancer, non alcoholic fatty liver disease (NAFLD), and depression [7]. However, obesity, beyond its direct impacts on the health status, seems to affect indirectly the child as well. Especially, maternal pre-pregnant obesity probably affects the fetus and the fetal growth in its initial stage of life, neonate at birth, as well as the child in its later development. Many studies have focused on the above mentioned issue by studying the impact of maternal obesity on the health status and the anthropometrical characteristics of the child.

Many studies have already focused on maternal obesity and its outcomes in both pregnancy and perinatal period correlating maternal BMI to higher incidence of pre-eclampsia, hypertension, gestational diabetes, cesarean section, macrosomia, congenital malformations, and miscarriage [8]. Gravidity of an obese woman is integrated in high risk pregnancies due to higher frequency of specific complications either for the mother or neonate. For this reason, obese patients are advised to be primarily hospitalized in a hospital unit fitted with experienced obstetric team and Neonatal Intensive Care Unit (NICU).

The main objective of this article is to review data, from 2000 to 2010, that correlated maternal obesity to obstetrical outcomes as well as neonatal and later child-life health problems. To our knowledge, there are no studies that summarize the effect of maternal obesity of women with no other medical pre-existing health problems- such as diabetes mellitus-, on obstetrical, neonatal, and especially childhood and adult life health problems. All the available published data that explored the later stages of life of descendants of obese mothers were reviewed, in a way to prepare the ground for any future studies which might investigate in depth the whole matter or could have a counseling character for managing obese pregnant women.

2. Methods

Pubmed search was performed using the words "maternal obesity or maternal elevated BMI and obstetrical-neonatal outcomes/implications, cesarean section, hypertensive disorders, mortality, fertility, miscarriage, Apgar score, NICU admission, preterm delivery, malformations, birthweight, mortality, asthma" and revealed almost 250 studies.

Only 95 studies (38%) met the preset criteria and were included in this review. Reference list of all the studies were checked for identifying additional relevant studies. All the studies, included in this review, refer to singleton pregnancies and the majority of them focused on nulliparous women. Studies that refer to patients with diabetes mellitus (in pregnancy, type 1 or type 2) were excluded since hyperglycemia influences health status of both the mother and the child. Additionally, in the studies, where women with diabetes were included in the study population, only the results statistically adjusted for this parameter were presented. In a paper, diabetes mellitus was not considered as a risk factor to the variables under investigation, since there was no direct relationship between them [10]. Running through a plethora of studies considering obesity during pregnancy, many studies published earlier than year 2000 were considered. Only four of them were included in our study because they were considered as benchmarks in many subsequent studies and also many pathophysiological pathways were presented there. Data were not limited to European countries and also USA and other subpopulations were included, in an effort to present a global approach to the subject. All the selected studies were published in peer-reviewed medical journals or electronic libraries presented in Pubmed database. All the studies in a language other than English were excluded.

The majority of the studies identified and categorized patient's obesity using BMI (kg/m^2). According to WHO, someone is identified as "Normal weight" when BMI is 18.5–24.99 kg/m^2, "Overweight" when BMI is 25–29.99, and "Obese" when BMI is 30 or more. Obesity is further sub-classified into: category I (BMI = 30–34.99), category II (BMI = 35–39.99), and category III (BMI is ≥ 40); which is also known as "morbid obesity". In a few studies, the defining borders of obesity were not clear. BMI was measured in the pre-pregnancy period or in early pregnancy [first weeks up to first trimester]. All the studies that classified obesity

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using a different method than BMI, such as skin thickness, were excluded.

Birth weight of the newborn was categorized using percentile curves for gestational age and sex. Neonates above 90th percentile were considered as large for gestational age (LGA), between 10th–90th were considered appropriate for gestational age (AGA), while under 10th percentile were considered small for gestational age (SGA). Macrosomic neonates were identified when birth weight exceeds 4000 grams. In some studies, the threshold was higher, up to 4500 grams. Standardized tables for weight in relation to sex and age are used to identify childhood obesity. When a child weight exceeds the 95th percentile, he/she is identified as obese [9].

Fetal death is defined as miscarriage that occurs before 20 weeks of gestation or with fetus weight <500 grams. Perinatal death includes miscarriages beyond 20 weeks of gestation or >500 grams of fetus or neonatal death up to the 7th day after birth. Neonatal death is considered as death of a live born neonate up to 28 days after delivery. Stillbirth is defined as a delivery of a dead fetus at or after 28 completed weeks. Gestational age was defined by last menstrual period and corrected by following ultrasonography, when applicable. Preterm birth is considered when delivery occurs before 37 weeks of gestation. Most of the studies focus on late preterm deliveries (at 34–36 weeks of gestation), although very preterm deliveries (<32 weeks of gestation) are also included.

3. Results

3.1. Obstetrical outcomes

3.1.1. Hypertensive disorders

One of the major problems during pregnancy is hypertensive disorders that may occur through the 2nd trimester (>20 weeks of gestation). In terms, hypertension, preeclampsia (hypertension accompanied by proteinuria) and in more severe cases eclampsia afflicts this subgroup of population. In contrast to normal weight mothers, increased incidence of pregnancy related hypertensive conditions is observed in overweight, obese and morbidly obese patients [10]. Based on a study of 11252 women in Queensland, hypertensive disorders presented in 5.6% of the study population. Rates of hypertensive disorders significantly increased in overweight women (OR = 1.74 [95% CI: 1.45–2.15]; it was more frequently diagnosed in obese (9.1%), OR = 3 [95% CI 2.40–3.74] and morbidly obese women (14.5%), OR = 4.87 [95% CI: 3.27–7.24] [11]. Likewise, in an analysis included 287213 pregnancies over an 8-year period in London, preeclampsia was noted in 0.7% of women with BMI 20–25 which was clearly less than overweight women (0.97%, OR = 1.44 (99% CI: 1.28–1.62), and obese women (1.43%, OR = 2.14 (99% CI: 1.85–2.47) [12].

The above results are reinforced by many studies around the world. In a study in Abu Dhabi, morbid obese women were at greater risk of having pregnancy-induced hypertension, compared to normal weight women ($p < 0.001$) [13]. In Canada, researchers reported a very strong correlation between gestational hypertension, preeclampsia, and maternal BMI. The ORs for hypertension were 1.56 for overweight (CI: 1.35–1.81), 2.01 for obese (CI: 1.64–2.45) and 2.77 (CI: 1.60–4.78) for morbidly obese women. In order to realize the exact impact of obesity in hypertension disorders, we compared the ORs of preeclampsia, which were 2.28 (CI: 1.88,2.77), 4.65 (CI: 3.71–5.83) and 6.26 (CI: 3.48,11.26) for normal, overweight, obese, and morbidly obese respectively [14]. The incidence of hypertensive complications (pregnancy related hypertension and preeclampsia) in overweight and obese women was 3-fold increased (13.2%) and 4-fold increased (16.7 %) respectively in comparison with normal weight patients (5.7%) $p < 0.001$ [15].

Also, it was remarkable the increase of the incidence of preeclampsia, from 6.7% in normal weight patients up to 21.2% in morbid obese patients (BMI > 35) ($p < 0.001$) [16], with a difference of about 14%. Strong correlation of preeclampsia and obese women, was also noted by Athukorala et al. ($p < 0.0001$). Moreover, Athukorala et al. highlighted the greater rates of pregnancy-induced hypertension, even when distinguishing the study group in overweight, OR = 1.94 (95% CI: 1.43–2.65) $p < 0.0001$, and obese patients, OR = 3.19 (95% CI: 2.36–4.30), $p < 0.0001$ [17].

In a study that included 508926 singleton pregnancies, there was a statistically significant difference ($p < 0.001$) between normal weight and morbidly obese pregnant women. Hypertension was identified in 17.1% of morbidly obese patients type I (BMI 40–44.99) and in 23.3% of morbidly obese patients type II (BMI > 45) in contrast to 1.2% of normal weight women. The incidences of preeclampsia and eclampsia were 16.5% and 23.3% in morbid obese patients

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type I and II respectively compared to 1.6% in normal weight [18].

3.1.2. Fertility

There are quite a few reported studies emerging the association between increased BMI and subfertility. The actual mechanism of this association is not well known. However, ovulatory dysfunction due to increased levels of androgens, insulin secretion and insulin resistance seems to play a crucial role in this phenomenon. More precisely fat input in the abdominal area (apple body-type) seems to have a greater impact on endocrinological disorders. Many observational researches support weight loss as the initial therapy approach for infertility in obese patients [19]. It is estimated that 10–15% weight loss in overweight patients, leads to 30% spontaneous pregnancy and up to 50% to drug-induced pregnancy [20].

A study of 100 normal-weight women and 100 morbidly obese women (BMI > 35) reported sub-fertility rates of 2% and 12% respectively ($p = 0.005$) [16]. Regarding the role of weight loss in improvement of fertility, 47% of women who undertook a biliopancreatic diversion, and were considered infertile preoperatively, achieved pregnancy after surgery [21].

3.1.3. Caesarean section

According to literature, it seems to be an indisputable positive linkage between incidence of caesarean delivery and obesity. This is heightened by the reproducibility of the results in both overweight and obese patients. In a population based screening study, in USA, including 5142 primiparae women, an increased caesarean delivery rate among obese (33.8%, OR = 1.7) and morbidly obese patients (47.4%, OR = 3) compared to the control group ($p < 0.01$) has been reported. In this study, the control group consisted of normal weight as well as overweight women in order to describe in a more consistent way the typical USA obstetric population [22]. Roman et al. performed an aged and parity matched study between 2081 obese women and 2081 normal weight women. Cesarean section was more frequently performed in obese patients 25.2% ($p = 0.001$) than in control group (15.1%) [23]. Similar results were reported in another study, where obese women were more likely to undergo a cesarean section compared to non obese patients (normal weight and overweight) [24]. Additionally morbidly obese patients are even more probable to undergo a cesarean section compared to normal weight women ($p < 0.05$) [13].

Overweight and obese pregnant women were more likely to undergo a caesarean section and more precisely there is a dose-dependent effect regarding high maternal BMI and cesarean section [11, 17]. Specifically, for one unit increase in maternal prepregnancy BMI, the odds for cesarean section were increased by 7% [10, 25].

In many studies, researchers found an increased incidence of cephalopelvic disproportion and premature placenta abruption situations that are "absolute" indications for cesarean section. As a result the indirect incidence of cesarean section increases in obese patients with these pre-mentioned pregnancy complications [12, 16, 18, 22, 26].

3.1.4. Maternal mortality

Over the last decades, maternal mortality in developed countries shows a decreasing tendency due to medical and pharmaceutical evolvement as well as to early diagnose and treatment of each pregnancy complication. There are few studies that examine the relationship between maternal pre-pregnant obesity and mortality. Maternal pre-pregnant BMI was strongly associated with maternal mortality. This correlation was statistically significant for overweight patients with BMI > 27 [OR = 1.55 (95% CI: 1.06–2.28)] as well as for the obese ones [OR = 2.02 (95% CI: 1.24–3.28)] [27]. On the contrary to the previous results, another study showed no correlation between maternal overweight/obesity and maternal mortality or adverse outcomes [OR = 1.34 (95% CI 0.93–1.93)], $p = 0.12$ and [OR = 1.43 (95% CI 0.94–2.17)], $p = 0.10$ respectively [17].

3.2. Fetal neonatal and child outcome

3.2.1. Apgar score

In many studies, obesity before pregnancy is correlated to low neonatal Apgar score. In a retrospective study from Boston, USA, 58089 non-Hispanic white women and their children were studied in regard to maternal obesity and neonatal 5 min Apgar score. Obese mothers as well as morbidly obese mothers had a higher incidence of low neonatal Apgar score [4–6]. However, there was no significant important correlation between overweight patients and low

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Apgar scores. Moreover there was no association found between maternal weight and very low Apgar scores (<3) [28].

Additionally maternal overweight and obesity was correlated with low 5 min Apgar score (0–6) in a retrospective study of 465.964 pregnancies ($p < 0.001$ for overweight and obese patients) [29]. In accordance to these results, Nohr et al. observed low 5 min Apgar scores (<8) in neonates of overweight and obese women [30]. Also, in Finland, a clinically and statistically important difference in 5 min Apgar scores, depending on maternal weight status was reported. The rate of low Apgar score (<7) in overweight patients was 2.5% ($p < 0.001$) and the rate in obese and morbidly obese patients was 2.6% ($p < 0.001$). Briese et al who studied 508926 singleton pregnancies, observed a 3-fold increase in low 5 min Apgar score (<4) between normal weight and morbidly obese patients. The rates were 0.3% in normal weight, 0.9% in patients with BMI > 40 and 0.8% in BMI > 45. For Apgar scores of 4–7 the rates were 1.8%, 3.4% and 4.6% respectively [18]. By limiting investigations to 5 min Apgar scores <3, Abenhaim et al. showed greater frequencies of low scores as BMI increases [14]. However, in a cohort study of 2049 pregnant patients, using linear regression analysis, 5- and 10-minute Apgar scores did not correlate with maternal BMI [15]. Furthermore, the rate of low 5-minute Apgar score (score <4) in overweight and obese patients did not differ from normal weight patients ($p = 0.76$, $p = 0.89$) [17].

3.2.2. *Neonatal admission to intensive care unit [NICU]*

There are several studies that examine the relationship between maternal BMI and neonatal admission to NICU, most of which, found a clear positive correlation between them. Raatikainen et al. found a proportion of NICU admissions, 9.7% in neonates of overweight patients and 12.0% in neonates of obese and morbid obese patients ($p < 0.001$).

The same trend was seen in the study of Callaway et al, where admission to NICU was 4.0% for neonates of overweight women, 5.3% for neonates of obese and 10.9% for neonates of morbidly obese women ($p < 0.001$). However, the results were statistically significant only for morbid obese mothers with adjusted OR 2.77(1.81,4.25) [11]. Also Kumari stated morbid obesity as an independent and remarkable risk factor for neonatal admission to NICU ($p < 0.001$) [13]. Additional studies supported that neonates of overweight and obese women [15], as well as those of morbid obese women [14], are at high risk of being admitted to NICU. Especially, the risk is positive even for overweight patients with OR = 1.22 (99% CI: 1.16,1.28) [12].

On the contrary, there is no statistical important difference supported, between maternal BMI and neonatal recovery in NICU ($p = 0.96$), with cumulative incidence 6.5% in both obese and normal weight women [23]. Similarly, other studies, investigating the relationship of overweight or obese pregnancies with NICU admission, either found no differences between these groups or did not show any statistical importance [17].

3.2.3. *Preterm delivery*

The issue of preterm delivery is controversial and it is not clear whether it is due to obesity or other unremarkable reasons that lead to the onset of labor. A statistically significant risk for preterm delivery in women with high BMI was reported by several studies (Table 1) [11, 14, 22, 31].

On the other hand, many researchers do not accept a strong positive relationship between preterm delivery and maternal BMI since there is no remarkable statistical significance (Table 1) [12, 17, 23, 26, 32].

In a recent study of Zhong et al. of the preterm labor induction, prepregnancy obesity was correlated with lower rates of spontaneous preterm delivery without PPROM before 37 weeks, while-at the same time-the incidence of Preterm Premature Rupture of Membranes (PPROM) <37 and <34 weeks in obese patients was increased [33]. A couple of other investigators support a lower risk, up to 10%, for preterm delivery in overweight and obese patients [26, 34] as well as in morbid obese ones [13]. Finally, obesity and morbid obesity in African American women leads to decreasing incidence of preterm delivery [32], although Wise et al. suggested that obese African American women are at greater risk for medically-indicated preterm delivery [35].

3.2.4. *Congenital defects*

Birth defects are caused by both genetic and environmental factors. Maternal obesity has been identified as an independent risk factor for neonatal malformations. There are several researches that correlate elevated BMI to specific anomalies.

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Table 1
Maternal BMI and preterm delivery

	Studies	BMI	Preterm delivery	OR		CI %	P
Significant	Abenhaim et al. [14]	25–29,9	32–36 w	1.20	95	[1.04,1.38]	
		30–39,9		1.60	95	[1.32,1.94]	
		≥40		2.43	95	[1.46,4.05]	
	Callaway et al. [11]	>40	<34 w	2.13	95	[1.13,4.01]	
	Weiss et al. [22]	≥35	<37 w	1.5	95	[1.1,2.1]	
	Cnattingius et al. [31]	≥30	<32 w**	1.6	95	[1.1,2.3]	
Non significant	Roman et al. [23]	>30	<37 w	0.8	95	[0.6,0.97]	0.03*
		>30	<34 w	1.2	95	[0.8,1.7]	0.32
	Sebire et al. [12]	25–30	<37 w	0.82	99	[0.78,0.86]	
		>30		0.93	99	[0.87,1.00]	
		25–30	<32 w	0.73	99	[0.65,0.82]	
		>30		0.81	99	[0.69,0.95]	
	Briese et al. [26]	≥30		0.47	95	[0.43,0.51]	<0.001‡
	Athukorala et al. [17]	25– 29,9	<37 w	0.97	95	[0.62,1.51]	0.90
		≥30		1.24	95	[0.77,2.01]	0.37
	Aly et al. [32]	30–39	<37 w	1.15	95	[0.99,1.33]	0.01*
		≥40		1.4	95	[1.08,1.82]	0.01*

*$P<0.05$; †$P<0.01$; ‡$P<0.001$; §$P<0.0001$; **for primiparae women only.

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3.2.4.1. Heart malformations

In a case-control study, 7392 neonates with congenital heart defects were examined and compared to 56304 controls, regarding their mothers' weight status. The outcome of giving birth to a child with a major congenital heart defect among obese and morbidly obese mothers, reached statistical significance, $p=0.004$ and $p=0.0001$ respectively. In fact, children of obese and morbid obese patients were at higher risk for developing all congenital heart defects (left and right ventricular outflow tract obstruction defects, atrial septal defects, hypoplastic left heart syndrome, aortic stenosis, pulmonic stenosis, and Fallot's tetralogy). However, neonates of overweight patients have a tendency to Fallot's tetralogy and not any other abnormalities. It has been shown that neonates of overweight women have less frequently total anomalous pulmonary venous return ($p=0.02$) and double outlet right ventricle ($p=0.046$). In general, the more maternal BMI increases, the greater ORs for having a congenital cardiovascular anomaly, are observed [36]. Similar results were reported by several other studies [37, 38]. In one of these, including 6081 neonates with congenital heart defects and comparing them with 812457 controls and their mothers, it was demonstrated that neonates of obese mothers were at higher risk of having a cardiovascular defect (except complex severe defects). Conversely, neonates of overweight women did not have a tendency towards cardiovascular abnormalities [38].

Although there is no sufficient data concerning African American overweight and obese women (BMI ≥ 27), their neonates tend to have a higher incidence of cardiac malformations [39].

It is remarkable that all women over the normal BMI (>25) show higher incidence to acquire descendants with heart defects [tetralogy of Fallot, total anomalous pulmonary venous return, hypoplastic left heart syndrome, Ebstein's anomaly right ventricular outflow tract return (pulmonary valve stenosis), and septal defects (sequndum atrial septal defect)] [40].

3.2.4.2. Other malformations

Many researchers have found a positive relation between maternal obesity and special birth defects, such as anencephaly, spina bifida, anorectal atresia, hypospadias, limb reduction, diaphragmatic hernia, and omphalocele, of their neonates [41–43].

In Callaway's et al study, birth defects for obese and morbid obese mothers reported a high significance rate in contrast to overweight women whose rates did not achieve statistical significance [11]. Additionally, it was showed that neonates of obese mothers are at higher risk of having birth defects such us spina bifida (unadjusted OR 3.5 [95% CI 1.2, 10.3]), omphalocele (OR 3.3 [95% CI 1.0, 10.3]), and multiple anomalies(OR 2.0 [95% CI 1.0, 3.8]) compared to neonates of normal weight women. In another study, maternal obesity as well as morbid obesity were correlated to bilateral renal agenesis and renal hypoplasia [44].

There are some specific studies in which elevated maternal BMI (≥28) was not associated with major congenital anomalies (all together), while craniofacial and musculoskeletal defects (orofacial clefts, club foot, cardiac septal defects, hydrocephaly, and abdominal wall defects) are observed frequently in obese patients [45].

On controversy, only few studies support that malformations in living neonates are not correlated to maternal obesity as no statistically important difference was found between obese and normal weight patients [23].

3.2.5. Birth weight

It is supported that obese pregnant women are more likely to give birth to a macrosomic neonate. This fact is attributed to neonatal hyperglycemia and hyperinsulinemia (due to elevated maternal glucose levels) which accelerates fetal growth [46]. All the researchers recognize the correlation between maternal obesity and high birth weight (Table 2) [10, 12–17, 22–24, 26, 30, 47–49].

Similar results, but focused on the precise birth weight of the neonate, had Hincz et al. who correlated maternal obesity to a higher mean birth weight (3266 ± 929 g) in contrast to the control group-normal weight mothers- (3100 ± 751 g) ($p < 0.05$). Especially, they suggested that an increase of 1 kg/m^2 in maternal BMI, increases the relative OR by 1.1 [49]. On the other hand, some studies suggest that the relative risk for producing an SGA neonate decreases with maternal BMI increase [23, 30].

3.2.6. Weight status of child after birth

Although maternal obesity and neonatal birth weight have been studied extensively, the relation between maternal obesity and weight status of the child in its later life has not been studied thoroughly. It is estimated that high birth weight leads to a higher BMI during adolescence so it is suggested that intrauterine environment plays a potential role in anthropometric characteristics of the child [50].

Few studies correlate maternal high prepregnancy BMI to their children weight status after birth. In a prospective study, maternal BMI was correlated to child's weight and BMI in 14 months. More precisely, one unit increase in mother's BMI leads to an increase of 19 grams in child's body weight [10–28] and in an increase of 0.034 kg/m^2 in BMI. No association was found between maternal BMI and height of the child at 14 months [51]. This risk seems to exist in the 2nd, 3rd and 4th year of age, as well as in the 1st and 5th year [49, 52], since obese mothers tend to have obese children [53]. A recent research reported that maternal obesity has also an influential role on children's BMI at 7th year of age [54], as well as at 11th and 15th year (respectively) [52, 55]. Likewise children adiposity at the age of 9 years, increased along with maternal prepregnancy BMI [56].

Along with the previous, some researchers continue up to adult life in order to find a possible relationship between maternal BMI and child's weight status. Furthermore, tracking of childhood obesity in adult life is supported by several researchers. Especially the risk for obesity gets stronger when it refers to boys of obese mothers [55].

Moreover, in a population sample of 261 women, a follow up study was conducted, using the standard statistical methods compared with quantile regression methods in order to define any influence of maternal BMI on predicting adult body size. Maternal prepregnancy BMI was proved to be an important factor for predicting BMI at age of 20 years-except 90th percentile- and also at age of 40 years-especially for lower quantiles [57]. Additionally, there seems to be a positive correlation between obesity in adulthood and increased childhood BMI simultaneously with the increase of maternal BMI in early pregnancy [52].

3.2.7. Children morbidity

Hypoglycaemia is recognized as a frequent pathology for neonates of obese mothers [11, 15]. Moreover, neonates of obese mothers tend to have difficulties in feeding. Researchers also noted that these neonates were unable to maintain a stable body temperature so incubator was indispensable [24]. Additionally, neonates of morbidly obese mothers have higher postnatal morbidity such as jaundice, generalized infection, asphyxia, hypoxia, cyanosis, hypoglycemia, and electrolyte disturbance [11, 18].

Infant adiposity [skin-fold thickness] at 12 and 24 months of age was correlated to maternal prepregnancy BMI [49]. Maternal obesity is strongly associated to elevated systolic blood pressure at age of 5 and metabolic syndrome in infancy (6–11 years) ($p = 0.039$) [58, 59]. This statement could be explained by the results of Catalano et al. who supported that insulin resistance develops primarily, during intrauterine life, in fetuses of obese mothers [60]. Finally

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Table 2
Maternal obesity and neonatal birthweight

Results	Study										
	MCRS-BW kg/percentile	SS	NSS	LGA		OR MCRS-OV	OR LGA-OV	OR LGA-O	OR MCRS-O	CI %	OR MCRS – MO
				SS	NSS						
Usha Kiran et al. [24]	>4	O							2.1 [1.6,2.6]		
Baeten et al. [10]	≥4	OV,O				1.5 [1.4,1.6]			2.1 [1.9,2.4]	95	
Abenhaim et al. [14]		OV,O	MO, SGA,IUGR			1.66 [1.23,2.2]			2.32 [1.58,3.41]	95	
Kalk et al. [15]	>4	OV,O	SGA	OV, O		1.54 [1.06,2.24] $p<0.05$	1.62 [1.14,2.32] $p<0.05$	2.57 [1.64,4.04] $p<0.001$	2.07 [1.25,3.42] $p<0.05$	95	
Ong et al. [49]	>90th	Maternal BMI									
Athukorala et al. [17]	>4.5	O	SGA both, overweight-macro-somic,	O	OV			2.08 [1.47,2.93] $p<0.0001$§	4.54 [2.01,10.24] $p=0.0003$‡	95	
Nohr et al. [30]				OV, O			1.7 [1.6,1.8]	2.9 [2.7,3.2]		95	
Weiss et al. [22]	>4.5	O,MO	IUGR						2.0 [1.4,3.0] $p=0.0006$‡	95	2.4 [1.5,1.38] $p<0$, 01
	>4								$p<0.0001$§		$p<0.01$
Sebire et al. [12]	>90th	OV,O	<5 percentile			1.57 [1.50,1.64]			2.36 [2.23,2.50]	99	
Pathi et al. [16]	>90th	O							$p<0.001$‡		
Kumari [13]		MO								95	$p<0.001$
Briese et al. [26]	≥4	O							2.16 [2.05,2.28] $p<0.001$‡	95	
Roman et al. [23]	>4	O	<2,5 kg, SGA	O				2.4 [1.9,2.9] $p<0,001$‡	3.1 [2.2,4.3] $p<0.001$	95	

BW = birth weight, MCRS = macrosomia, SS = statistical significance, NSS = no statistical significance, OV = overweight, O = obese, MO = morbid obese.

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maternal obesity was correlated to a higher risk of coronary heart disease in the male child [61].

3.2.8. Respiratory problems - asthma

There are serious implications that maternal obesity is associated with respiratory problems and asthma in childhood. The hypothesized cause is that maternal obesity influences in early stages fetal lung development as well as fetal immune system. In a birth cohort study, researchers investigated the conflicting relation between maternal prepregnancy BMI and the incidence of asthma up to the age of 8 years. Although there seems to exist an adjusted association between maternal obesity and asthma, at 8 years, with borderline significance (OR 1.46 (95% CI: 0.97– 2.18) $p = 0.067$), this correlation gets stronger and statistically important in children with a predisposition for asthma. Specifically, the more maternal BMI increases the higher is the risk for developing asthma. However, there is no correlation between maternal overweight and asthma in children in the absence of predisposition factors [62].

Furthermore, taking into consideration a Norwegian study, including 33.192 children up to 18 months of age, there is a relationship between wheezing and maternal obesity [63]. Under circumstances, wheezing in early infancy is related to asthma during childhood [64–68], and in this way maternal obesity may be indirectly related to children's asthma. In detail, there is a linear increase of wheezing getting along with increasing maternal BMI with the adjusted risk difference for overweight women 0.4%, and for obese women 3.3% ($p = 0.008$). The results revealed no effect of BMI on lower respiratory tract infections [63].

3.2.9. Children's mortality

Mortality, whether it takes place during intrauterine or perinatal period, and its association with maternal obesity, has been studied thoroughly.

3.2.9.1. Fetal and perinatal period

According to several reports, late fetal death (stillbirth after 28 weeks) is strongly associated with increasing maternal body mass index [12, 23, 31, 69, 70]. Furthermore, there is a study reporting that the risk is double for obese mothers to face fetal and/or neonatal death, despite the fact that this risk did not reach statistically significant level for overweight patients [71]. Another research specifies the higher risk of miscarriage during the first 6–12 weeks of gestation and also supports the elevated risk of recurrent miscarriages along with obesity (>3 miscarriages <12 weeks of gestation) [72].

On the other hand researchers, after comparing the risk of stillbirth and perinatal death between obese and non obese patients they found no statistically significant difference between them [11, 14, 17].

3.2.9.2. Neonatal period and early infancy

In a case-control study, researchers reported the impact of maternal obesity on later infant death (neonatal-until 28 days after labor and post neonatal-after 28 days but before first year). As a result, maternal obesity was linked to neonatal death, post-neonatal death and infant death while overweight was only linked to neonatal death [73]. Likewise, Thomson et al. recognize the same risk for obese and morbidly obese patients, although they did not support a relationship between overweight mothers and infant death [74]. In Baeten et al. study, infants of overweight and obese mothers had a higher incidence of mortality [10]. On the contrary, it is supported that overweight women have a lower rate of neonatal death compared to normal weight and morbid obese mothers.

4. Discussion

Pregnancy is a process with underlying endocrine physiology not entirely explored. It is supported that there is a 40–50% increase in insulin resistance during pregnancy [75]. When it comes along with obesity, which also, is not completely understood from the metabolic point of view, processes are more complicated. There is evidence suggesting a clear relationship between obesity, insulin resistance, lipid disorders, hypertension and development of type 2 diabetes [76]. The constellation of these clinical observations is widely known under the name "metabolic syndrome". According to recent studies, adipose tissue is active-secretory, playing a key role in regulation of metabolic reactions concerning glucose, free fatty acids, insulin through the action of mediating cytokines or releasing hormones such as leptin and IL-6. On the other hand, in the uterus, fetal growth and development is based upon two major factors; genetic substrate and maternal environment. The latter is perceived from fetus through signals transmitted by the placenta, such as nutrient transfer, cytokines and oxygen concentration. In pregnancy, because of the fact that in modern endocrinology obesity is thought to be a chronic

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inflammatory state, major alterations take part in the body, either systemically in blood vessels or topically via the placenta, liver and adipose tissue.

As a result, obese pregnant women, face a dysregulation of body homeostasis in multiple levels. Of significant importance are the circulating levels of different kinds of cytokines such as TNF, IL-1 and leptin which can modify the insulin signaling pathway between liver, muscles, and adipocytes in a way which leads to insulin resistance [77]. Resistance leads to higher concentration of metabolic fuels allowing excess of nutrients to be shunted to the fetus. This abundance enhances the fetal growth rates by up-regulating the expression of insulin-like growth factors [78], as well as the turnover of fatty acid transporters and thus affecting body size and composition [60]. Similarly, there is endothelial damage mediated via vasoactive adipokines, angiotensin, and endothelin. Vasomotor responses are impaired while there is dysfunction of fibrinolytic mechanism and coagulation [79]. As a result, obese pregnant women face a lower endothelium vasodilation [80]. These parameters in obese patients may contribute to maternal and fetal complications during pregnancy and it is hypothesized that they may influence fetal programming of adult vasculopathies [77].

Interestingly, the placenta acts as a manager controlling the release of various inflammatory markers [81], sensing the maternal environment and adapting to it in order to protect the fetus from the potentially hostile, inflammatory, hyperinsulinemic, and oxidative environment of the obese mother. Obesity is known to raise the number of immunoregulatory cells such as macrophages, n-k cells and dendritic cells gathered in the placenta [81]. Of note, obese pregnant patients gain weight in central compartments (apple-shaped) in contrast to lean women who gain weight in lower-body compartments (pear shaped). Central obesity is correlated to insulin resistance, lipotoxicity, inflammation and metabolic dysregulation. Such complications deteriorate the already overburdened metabolic profile of the obese patient [82].

There are many implications concerning the interactions between mother and fetus with a few plausible mechanisms but still a lot of investigatory research has to be conducted in order to come up with results revealing the exact pathophysiology between obesity, pregnancy and gestational complications [76].

Maternal overweight and obesity have been correlated in the past with obstetrical, neonatal and long-term complications [83]. Our study is an effort to find out what has been changed over a decade but also to shed more light into possible long term impact on children's health. In 2008, Guelinckx et al. analyzed the impact of maternal obesity in both mothers and neonates. Moreover gestational diabetes or/and obesity was correlated to higher rates of metabolic syndrome and obesity in childhood [84]. In our study diabetes and gestational diabetes was excluded in order to observe implications of obesity itself in mothers and children. A recent meta-analysis revealed a significant relationship between maternal obesity and cesarean delivery, instrumental delivery, maternal morbidity (hemorrhage and infection) and hospital admission (maternal hospital stay and NICU admissions) [85].

This review has demonstrated a clear negative impact of maternal overweight and obesity on several obstetrical and neonatal parameters. In accordance to previous reports [86, 87], overweight and obese patients face higher rates of subfertility and infertility. Moreover fertility treatment in obese patients is insufficient as conception is more difficult to occur in this subpopulation, and if pregnancy is achieved, the rates of miscarriage are quite elevated [87–93].

Pregnancy complications of maternal obesity include hypertension, pre-eclampsia, and eclampsia [3, 86, 87, 92, 93], and obese patients are more likely to undergo a cesarean section (elective/emergency). According to a systematic review and meta-analysis of Poobalan et al. the risk for cesarean section, especially emergency, increases in parallel with BMI increase [94].

Maternal obesity has an unclear impact on maternal mortality. Although in developed countries maternal obesity is the most common cause of death among pregnant women [95], there is not enough evidence for this and further investigation is needed.

Maternal overweight and obesity seems to play a potential role in anthropometric characteristics of the neonate as well as in neonatal health status. Neonates of obese patients have a higher postnatal morbidity (hypoglycemia, jaundice, generalized infection, asphyxia, hypoxia, cyanosis, low Apgar score), and so neonatal admission to NICU is more common in this group. Additionally, neonates of overweight and obese mothers have a tendency to be macrosomic and LGA [96, 97], when simultaneously, obese mothers have lower rates of having an SGA neonate. The positive correlation between maternal obesity and some of the above mentioned parameters (pre-eclampsia, LGA, cesarean

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section and low Apgar score) is enhanced by a recent study, where super morbid obese patients (BMI $\geq$ 50) were at higher risk for several pregnancy complications compared to all other BMI categories [98].

Specific congenital malformations are more common among neonates of obese mothers and neonatal mortality is higher in this group. Preterm delivery still remains a conflicting issue as the results of many research teams are in favor of the idea that obesity leads to premature labor while other studies state this relationship as insignificant.

Regarding later development of the child, maternal obesity seems to be a risk factor for respiratory health problems and asthma in early childhood. Furthermore, children of obese patients are more likely to be overweight and obese in infancy, adolescence and early adulthood, as metabolic syndrome develops primarily. Tracking obesity during transition from infancy to adult life has negative impact on child's health status while the vicious circle of obesity and obesity-related health problems is reiterated relentlessly.

4.1. Strengths-weaknesses

To our knowledge there are no recent studies that summarize the effects of maternal obesity in pregnancy and perinatal period as well as in childhood and later adult life. Efforts have been made to collect numerous studies that matched the criteria and to present all possible literature mentioned implications of maternal obesity. However, the studies were conducted under different circumstances (e.g. methods, statistical analysis, participants, exclusion criteria, and definitions) and for this reason it was not feasible to perform a meta-analysis including all the pre-mentioned parameters and implications.

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