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REVIEW ARTICLE

Maternal obesity: focus on offspring cardiometabolic outcomes

Alessandra Gambineri[1] · Alessandro Conforti[2] · Andrea Di Nisio[3] · Daniela Laudisio[4] · Giovanna Muscogiuri[4] · Luigi Barrea[4] · Silvia Savastano[4] · Annamaria Colao[4] · on behalf of Obesity Programs of nutrition, Education, Research and Assessment (OPERA) Group

Abstract

Several human and animal studies have demonstrated that cardiometabolic parameters in infancy, childhood, adolescence and even adulthood are negatively influenced by many factors besides energy imbalance. Interestingly, maternal weight excess both before and during pregnancy seems to be a negative determinant of metabolic and cardiovascular outcomes in the offspring. This review includes both human and animal studies and finally highlights the link between maternal obesity and cardiometabolic disorders in offspring.

Introduction

Obesity is the most prevalent metabolic disorder among adults, adolescents and children throughout the world. It is frequently associated with a set of other metabolic disorders such as insulin-resistance, hyperlipidemia, glucose intolerance, and hypertension, which together increase the risk of cardiovascular diseases in adulthood [1]. The energy imbalance derived from an incorrect lifestyle is considered the main impacting factor on obesity and on other metabolic disorders at any age. However, there may be other important causative factors, such as genetics, hormones, education, socio-economic background, and parental status [2].

In a recently published population-based study it has been demonstrated that parental obesity is the most important risk factor in offspring for overweight or obesity in adolescence [3]. Other studies have confirmed that parental body mass index (BMI) and, particularly the mother's BMI, is a trigger of overweight or obesity not only in adolescence, but also in childhood, infancy and even in adulthood, and that it is strongly correlated with other cardiometabolic risk factors [4]. Gestational weight gain (GWG) represents an important determinant of metabolic and cardiovascular outcomes in the offspring. Animal studies support the role of excessive GWG, as well as maternal gestational overnutrition, on offspring adiposity and on many cardiometabolic alterations later in life [5], thus emphasizing that nutritional and environmental imbalances in utero may make a significant contribution to offspring cardiometabolic outcomes.

This review analyses the current state of the art and highlights the link between maternal obesity both before and during pregnancy with cardiometabolic disorders in offspring from infancy until adulthood. Although the paper is organized as a systematic review of the literature on human studies, animal studies are also taken into account to discuss the mechanisms through which maternal obesity might increase the development of cardiometabolic alterations in offspring.

Methods

Human studies

Data source and search strategy

An electronic search of MEDLINE (PubMed) and SCOPUS was carried out up to February 2019. Combinations of the

✉ Alessandra Gambineri
alessandra.gambiner3@unibo.it

1 Endocrinology Unit, Department of Medical and Surgical Sciences, St Orsola-Malpighi Hospital, Alma Mater University of Bologna, Bologna, Italy

2 Department of Neuroscience, Reproductive Science and Odontostomatology, University of Naples Federico II, Naples, Italy

3 Department of Medicine, Operative Unit of Andrology and Medicine of Human Reproduction, University of Padova, Padova, Italy

4 Endocrinology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

following search terms were adopted: (offspring OR childhood OR children OR adolescent OR youth OR teenager) AND (overweight OR adiposity OR obesity OR weight gain OR weight change OR weight increase OR BMI OR body mass index OR blood pressure OR metabolic disease OR cardiovascular diseases OR metabolic syndrome OR diabetes OR insulin OR cholesterol) AND (pregnancy OR pregnant OR pregnancies OR gestational OR gestation OR gravidity). No language or time restriction was adopted. Case series, case reports, books, congress abstracts and "gray literature" were not included in the analysis.

Study selection

We included only studies in which cardiometabolic outcomes in infants, childhood and adulthood were evaluated in relation to maternal excessive body weight and gestational weight gain (GWG). A total of 3469 items were identified through the search. The titles and abstracts of papers were analyzed and 38 full papers were considered for the review. The study design of the human studies selected is described in Tables 1 and 2.

Human studies in infancy and childhood

The studies selected for this section are summarized in Table 1, where the study design, study population, and a brief description of the main results are provided. Most of the studies focused on the impact of maternal obesity in early and late childhood period, i.e., from 4 to 11 years old [6, 8, 12]. Body mass index (BMI) was the most used parameter to measure metabolic disorders in offspring [8–10, 13–19]. Other anthropometric indexes, i.e., weight-to-length ratio, waist-to-height ratio, or waist circumference, were also frequently evaluated [8, 9, 12, 20]. In some studies, body composition was assessed using dual-energy X-ray absorptiometry [8–11, 21–23]. Cardiometabolic status was assessed by measuring lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) [6–8, 10–12, 24, 25], glucose, insulin, and c-peptide at fasting [8, 10, 17, 24, 25] or, less frequently, post-prandial [7] or in response to oral glucose tolerance test (OGTT) [26], insulin resistance indexes, such as glucose-to-insulin ratio or homeostasis model assessment-insulin resistance index (HOMA-IR) [8, 12, 23, 27], and blood pressure [9, 10, 25, 26].

Overall, these studies demonstrate that the effect of maternal obesity on cardiometabolic outcomes in offspring starts during the first months of life [17, 20, 21, 24]. In a large cohort study involving more than 4000 cases, Margerison Zilko et al. observed that an excessive increase in GWG was associated with an increased risk of overweight in neonates, defined by a BMI ≥ 85 centile [17]. In line with these findings, Crozier et al. detected an increased fat mass, measured using dual-energy X-ray absorptiometry, in neonates whose mothers have a history of excessive GWG [21]. Interestingly, a more recent cohort study involving 753 neonates showed that maternal pre-pregnancy BMI (mppBMI) and GWG were both positively associated with fasting glucose levels and negatively with HDL-cholesterol levels and glucose-to-insulin ratio of neonates, regardless of neonatal adiposity [24].

More robust evidence is available for childhood cases, and many cohort studies have been published [6–23, 25, 26]. The largest one, conducted by Wrotniak and colleagues with more than 10,000 participants, reported that excessive GWG was associated with an increased risk of overweight in 7-year-old children, irrespectively of mppBMI [14]. Their study indicates that the overweight risk in childhood increases by 3% for every 1 kg of maternal GWG (OR: 1.02; 95% CV: 1.00–1.03).

This association between excessive GWG and overweight or obesity in childhood has been confirmed by many other cohort studies [9, 18, 23, 27], and it seems to be particularly evident when excessive GWG is combined with maternal smoking during pregnancy, a short period of breastfeeding or inadequate daily sleep in infancy [15, 19]. Other cohort studies demonstrated that also excessive mppBMI is associated with an increased risk of overweight or obesity in childhood [8, 9, 11, 16, 19]. In addition, the combination of excessive GWG with maternal pre-pregnancy overweight or obesity appears to be associated with early onset overweight in childhood [16].

Even paternal BMI was positively associated with fat mass in 6–11 year-old children [11, 22], but mppBMI showed a stronger association [11].

Interestingly, both excessive mppBMI and GWG were also associated with higher systolic blood pressure in early [10, 11, 18, 25] and late childhood [9, 19, 23, 27], with insulin resistance [7, 8, 11, 27] and with low HDL-cholesterol levels [8, 9, 23]. In addition, the earlier the appearance of excessive GWG, the higher the risk for children having an adverse cardiometabolic profile, such as high BMI or high systolic blood pressure [10, 13].

Accordingly, the evidence suggests that reducing excessive maternal body weight before or during pregnancy would help to reduce the risk of cardiometabolic disorders in infants and children [28, 29].

Human studies in adolescents and adults

The studies selected for this section are summarized in Table 2, where the study design, study population, and a brief description of the main results are provided.

Most of the studies focused on the impact of maternal obesity in early adolescence and adolescence [19, 27, 30–36],

Table 1 Human studies in infancy and childhood evaluating the impact of maternal obesity on cardiometabolic outcomes.

Ref.	N. subjects	M/F	Age	Main results
[24]	753	393/360	Neonates	mppBMI and GWG positively associated with glucose, and negatively associated with HDL-C and the glucose-to-insulin ratio of neonates at delivery, irrespective of neonatal adiposity
[17]	4496	2317/2179	Neonates AND 2–20 years	Excessive GWG associated with increased risk of LGA at delivery, and increased risk of overweight during childhood
[21]	948	496/452	Neonates (at birth) AND 4–6 years	Excessive GWG associated with greater fat mass in the neonatal period as well as at 6 years
[20]	482	247/235	Neonates AND 5 years	Excessive GWG (>18 Kg) or excessive mppBMI associated with neonatal fatness and with overweight in early childhood
[15]	1110	n.a.	3 years	Higher probability of developing overweight in childhood with the combination of the following risk factors: excessive GWG, smoking, inadequate daily sleep in infancy (<12 h/day) and breastfeeding duration <12 months
[18]	1044	530/514	3 years	Excessive GWG associated with higher BMI z score, higher sum of subscapular and triceps skinfold thickness, higher SBP, and higher risk of overweight at 3 years old
[7]	179	93/86	6–11 years	LGA increased the risk of metabolic syndrome at 11 years Maternal obesity (pregnancy BMI > 27 kg/m^2) increased the risk of metabolic syndrome between 6 and 11 years
[6]	751	384/367	8 years	Total-to-HDL-C ratio at 8 years positively associated with maternal pre-pregnancy obesity and rapid infant weight gain
[8]	89	37/52	6–11 years	mppBMI > 30 kg/m^2 was the strongest predictor of obesity and excess body fat mass in childhood which, in turn, were characterized by metabolic dysfunctions (higher SBP, lower HDL-C and higher insulin resistance)
[9]	5154	2532/2622	9 years	Greater mppBMI associated with greater adiposity, SBP and DBP at 9 years Greater GWG associated with greater BMI, waist circumference, fat mass, SBP and lower HDL-C at 9 years
[10]	5908	2949/2960	6 years	Higher early pregnancy GWG (until 13.4 weeks) associated with higher childhood BMI, fat mass and SBP and a clustering of cardio-metabolic risk factors Higher mid pregnancy GWG (from 13.4 to 29 weeks) associated with higher childhood BMI, fat mass and SBP Higher late pregnancy GWG (from 29 to 39 weeks) not associated with any childhood cardiometabolic outcome
[11]	4871	2444/2427	6 years	Higher mppBMI and higher paternal BMI associated with higher BMI, fat mass, SBP and insulin levels at 6 years mppBMI showed a stronger association than paternal BMI
[12]	313	172/141	10 years	Excessive mppBMI in combination with excessive GWG associated with increased BMI, HOMA-IR and fat mass (visceral and subcutaneous) in childhood These effects were mitigated in women with adequate GWG
[22]	4091	n.a.	9–11 years	Maternal and paternal BMI positively associated with offspring fat mass
[16]	1739	945/794	2–12 years	Excessive GWG (≥ 20.43 kg) in combination with maternal pre-pregnancy overweight or obesity associated with early onset overweight (at 2 years) Maternal pre-pregnancy overweight or obesity associated with late onset overweight (after 6 years)
[23]	1090	542/548	6–10 years	mppBMI positively associated with total fat, HOMA-IR, and SBP Higher GWG increased the risk of greater adiposity in childhood
[25]	1459	770/689	5–6 years	Higher mppBMI associated with higher waist-to-height ratio and higher SBP-to-DBP, regardless of post-natal weight gain
[19]	777	370/407	4–20 years	High mppBMI (≥ 30 kg/m^2) associated with increased risk of obesity in childhood, adolescence and early adulthood High GWG, combined with low duration of breast feeding and smoking during pregnancy, associated with increased risk of obesity in adolescence and early adulthood
[26]	905		7 years	Excessive GWG associated with greater BMI and insulin resistance in childhood
[14]	10,226	51/49%	7 years	Excessive GWG associated with increased risk of overweight in childhood
[13]	8494	4205/4289	2–4 years	Maternal obesity in the early pregnancy associated with an increased risk of obesity in childhood

Study design. All are prospective cohort studies, except refs. [13] and [14] that are retrospective cohort studies.

BMI body mass index, *DBP* diastolic blood pressure, *HDL-C* HDL-cholesterol, *GWG* gestational weight gain, *HOMA-IR* homeostatic model assessment of insulin resistance, *LGA* large for gestational age, *mppBMI* maternal pre-pregnancy BMI, *SBP* systolic blood pressure, *total-C* total-cholesterol.

with only a few longitudinal studies until adulthood [37, 38]. BMI was the parameter most used to measure metabolic disorders in offspring [19, 27, 30–41]. Other anthropometric indexes, i.e., skinfold thickness, waist-to-hip ratio, or waist circumference were also frequently evaluated [30, 32, 36–38, 40, 41]. In some studies, body composition was assessed using bio-impedance [39]. Cardiometabolic status was assessed by measuring the lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) [32, 40], glucose, insulin, and c-peptide at fasting [30, 32, 40], insulin resistance indexes, such as glucose-to-insulin ratio or HOMA-IR [30, 32], or blood

Table 2 Human studies in adolescents and adults evaluating the impact of maternal obesity on cardiometabolic outcomes.

Ref.	N. subjects	M/F	Age	Main results
[33]	4452	2606/2642	11	mppBMI and maternal weight at the end of pregnancy positively associated with both SBP and DBP in early adolescent subjects of both sexes
[34]	11,994	5583/6411	9–14	GWG positively associated with adolescent BMI
[30]	1392	706/686	17	mppBMI positively associated with adolescent BMI, WC, WHR, SBP, fasting insulin and glucose levels, and HOMA-IR levels. GWG in early-pregnancy, but not in mid-pregnancy, positively associated with adolescent BMI, WC and WHR
[31]	295	145/150	18	Excessive GWG found to be a risk factor for overweight or obesity in adolescence, as a function of mppBMI. In particular, GWG had a greater impact on offspring obesity if mppBMI was <76th percentile; if GWG was categorized according to IOM guidelines, overgain predicted offspring overweight if the mppBMI was between the 29th and 83rd percentiles
[35]	26,506	F	18	Females whose mothers had a ppmBMI of 29 kg/m^2 had a 6.1-fold increased risk of obesity at age 18
[19]	777	370/407	19–20	Maternal pre-pregnancy obesity and excessive GWG found to be risk factors for obesity in early adulthood (Relative Risk of 6.4 and 2.1, respectively)
[32]	308	120/188	20	In normal-weight pre-pregnancy mothers, a weak positive association between the first 30 weeks GWG and offspring BMI was observed GWG positively associated with fasting insulin and HOMA-IR in male offspring
[27]	2271	1134/1137	21	GWG positively associated with offspring BMI and SBP
[36]	2978	1533/1445	23	mppBMI positively associated with offspring BMI and WHR
[37]	4234	2218/2016	1–42	GWG positively associated with offspring BMI at all ages and with WC at age 42 years
[38]	6280	2876/3404	1–32	Maternal pre-pregnancy overweight or obesity associated with higher BMI of offspring at any age and with higher prevalence of overweight or obesity at age of 32 years Maternal BMI positively associated with WC and WHR at 32 years
[41]	276	112/164	30	Higher maternal BMI at the first antenatal visit and higher GWG independently associated with higher percentage of body fat of offspring
[40]	1256	622/634	32	mppBMI, independently of GWG, positively associated with BMI, WC, SBP, DBP, fasting insulin and triglycerides, and negatively associated with HDL-C in offspring GWG, independently of mppBMI, positively associated with offspring adiposity
[42]	37,709	19,415/18,294	34–61	Offspring of obese mothers (BMI > 30 kg/m^2) had an increased risk of hospital admission for cardiovascular events with respect to offspring of normal-weight mothers (risk ratio, 1.29; 95% CI, 1.06–1.57)
[39]	2003	NA	62	Maternal BMI positively associated with BMI in the offspring. Maternal BMI positively associated with percentage of body fat in offspring

Study design. Prospective cohort studies, except refs. [34, 35, 39–41] and [42] that are retrospective cohort studies.

BMI body mass index, *DBP* diastolic blood pressure, *GWG* gestational weight gain, *HDL-C* HDL-cholesterol, *HOMA-IR* homeostatic model assessment of insulin resistance, *mppBMI* maternal pre-pregnancy BMI, *SBP* systolic blood pressure, *WC* waist circumference, *WHR* waist-to-hip ratio.

pressure [30, 32, 33, 40], and also cardiovascular events [42].

The BMI as well as systolic and diastolic blood pressure of cohorts of early adolescents were positively associated with mppBMI [33] and GWG [33, 34]. Similar results were found by analyzing cohorts of late adolescents in which BMI was positively associated with GWG in the early phase of pregnancy, whereas systolic blood pressure, fasting insulin and glucose levels, and HOMA-IR other than BMI were positively associated with mppBMI [30].

This positive association between mppBMI or GWG and BMI in offspring was confirmed in many other epidemiological studies performed in adults [36, 37, 40], where it was also demonstrated that higher maternal BMI at the first antenatal visit and higher GWG were independently associated with a higher percentage of body fat of offspring at 30 years [41]. In addition, excessive mppBMI and GWG were found to be risk factors for overweight or obesity of offspring in adult age in many other studies [19, 31, 35, 38]. In particular, daughters of women with a mppBMI above 29 kg/m^2 showed a 6.1-fold increased risk of obesity at age 18 [35]. In addition, one long-term prospective cohort study on offspring with a follow-up examination from 1 to 42 years of age demonstrated that at the age of 42, the risk of obesity was significantly related to the GWG (OR 1.08 per kg GWG) [37].

In another long-term prospective longitudinal study, the authors demonstrated that maternal overweight or obesity before pregnancy was associated with higher BMI in offspring at all ages, from childhood until adulthood, suggesting that excessive maternal BMI represents a persistent risk factor for lifelong obesity [38]. Accordingly, the

positive association between maternal BMI and offspring body fat also persisted in old populations, as supported by a cohort study where 2003 individuals aged 62 years were evaluated with the finding that maternal BMI was positively associated with offspring body fat percentage [39].

Few data are available on the association between mppBMI or GWG and cardiometabolic factors in offspring during adulthood. However, the data that are available demonstrate a significant association between mppBMI or GWG and cardiometabolic risk factors, in particular systolic and diastolic blood pressure, insulin levels, insulin resistance, and adverse lipid profile in early adulthood [32, 40]. Interestingly, Mamun et al. [27] demonstrated that the systolic blood pressure of offspring at 21 years was 0.2 mmHg higher for each 0.1 kg/wk increase of GWG in the mother [27].

Finally, a very large cohort analysis from birth records for a population of 37,709 subjects, demonstrated that the offspring of mothers with increased BMI experienced significantly more hospital admissions from all cardiovascular events combined [42]. The observed associations were independent of several confounders, including maternal social class, maternal parity, and current age and sex of offspring.

Altogether these results suggest that the intrauterine environment has a crucial and long lasting role on the risk of developing premature cardiovascular risk factors and cardiovascular events in offspring.

Animal studies

The animal studies confirmed the findings of human studies and added information on the mechanisms through which obesity during pregnancy might increase the development of cardiometabolic alterations in the offspring.

The studies performed in rodents confirm that maternal obesity is associated with increased adiposity, hypertension, dyslipidemia, and altered glucose tolerance in offspring. They also demonstrate that there is a central leptin resistance at the level of the arcuate nucleus (ARC) with peripheral hyperleptinaemia [43].

Of particular interest is the negative impact of overnutrition with a high-fat diet during pregnancy in cardiometabolic outcomes of offspring. Several studies have in fact shown that offspring of high-fat diet overfeeding rats during pregnancy and lactation are characterized by obesity as well as by high blood pressure [44–46]. In particular, Samuelsson and colleagues compared the offspring of a group of female rats fed on a highly obesogenic diet (20% fat and 10% simple sugar; total energy density: 4.5 kcal/g) with a group of pregnant rats fed on a standard chow diet (3% fat and 7% simple sugar; total energy density: 3.5 kcal/g) for 5 weeks before and during pregnancy and lactation [45]. The authors observed that the offspring of rats fed on a highly obesogenic diet were significantly heavier, had greater fat pad weights, and had significantly higher basal night-time mean arterial blood pressure and serum leptin levels with respect to the offspring of rats fed on a standard chow diet [45]. These results led the authors to conclude that maternal obesity could induce hypertension in the offspring via an increased sympathetic drive in early development, which may be mediated by altered early life leptin signaling [47]. Selectivity in leptin resistance was hypothesized by the authors, with a resistance at the level of ARC, but with a preservation of leptin's sympathoexcitatory action in the cardiovascular-related ventromedial nucleus and dorsomedial nucleus of the hypothalamus.

More recently, Zhang and coworkers showed that a maternal high-fat diet modulates renin-angiotensin system (RAS), oxidative stress, and proinflammatory cytokines which, overall, alters angiotensin II and TNF-α actions in the brain and sensitizes the angiotensin II-elicited hypertensive response in adult offspring [48]. Several animal studies have also demonstrated that maternal high-fat feeding increases acid levels and produces dyslipidemia in the offspring [46, 49, 50]. Khan and coworkers showed that one-year-old chow-fed female rat offspring, born from mothers fed a high-fat diet, had high plasma triacylglycerol and reduced HDL-cholesterol levels [49]. Likewise, Maqsood and colleagues demonstrated that adult female offspring born from mothers fed a high-fat diet were heavier, fatter, and had raised serum total cholesterol levels with respect to those born from mothers fed with standard chow [46]. Maternal obesity or overnutrition during pregnancy in rats was also associated with the development of insulin resistance and/or glucose intolerance in offspring [51].

Interestingly, in animal studies maternal obesity is associated with important modifications of the fetal pancreas which appears to be of increased weight and with an increased number of insulin-positive cells per unit area [51]. Such morphological changes result in a premature postnatal β-cell loss and, later on, in a predisposition to the development of obesity and metabolic dysfunctions in adulthood [51]. The cardiometabolic profile of the offspring could also be influenced by epigenetic modifications of gene expression within the placenta as a consequence of maternal obesity [52]. In fact, several animal studies show that maternal obesity induces modifications in microRNAs, in histone, and DNA methylation, which have been associated with increased hepatic triglycerides in primates and altered mouse brain dopamine and opioid gene expression related to food behavior [53–55].

Overall, the animal studies suggest that programming obesity and cardiometabolic alterations in general could occur by permanent alteration of different pathways during early development.

Conclusion

This systematic review supports the notion that maternal obesity negatively impacts offspring cardiometabolic outcomes at any age. Excessive GWG seems to be a strong independent risk factor for overweight or obesity in infancy and childhood. Its effect is particularly evident when combined with other risk factors, such as maternal smoking during pregnancy, a short period of breast feeding, or inadequate daily sleep in infancy.

When excessive GWG is combined with excessive mppBMI, the probability for the children to develop early-onset overweight or obesity is high. Moreover, both excessive GWG and mppBMI seem to be similarly and significantly associated with an increased risk of overweight or obesity in adolescence or adulthood, and with an adverse cardiometabolic profile at any age. Obesity before or during pregnancy increases the risk of developing hypertension, hyperlipidemia, insulin resistance, and hyperglycemia during infancy, childhood, adolescence and adulthood. In adulthood an increased risk of cardiovascular events has also been reported.

Altogether these data emphasize that the intrauterine environment has a crucial and long-lasting role on the risk of developing obesity and premature cardiovascular risk factors and even cardiovascular events in offspring. This evidence suggests that the prevention of obesity, metabolic disorders, and of cardiovascular events should be considered before conception. Therefore, the correction of maternal obesity before pregnancy and the control of weight gain during pregnancy represent two important goals for the prevention of adverse cardiovascular outcomes in offspring.

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Compliance with ethical standards

Conflict of interest A Conforti received consulting fees from Merck Serono S.p.A. The remaining authors have nothing to disclose.

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