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http://informahealthcare.com/gye
ISSN: 0951-3590 (print), 1473-0766 (electronic)

GYNECOLOGICAL ENDOCRINOLOGY

Gynecol Endocrinol, 2013; 29(7): 626–631
 DOI: 10.3109/09513590.2013.777420

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Female obesity: short- and long-term consequences on the offspring

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Abstract

The worldwide prevalence of obesity has risen over the past few decades and women are currently more likely than ever to enter pregnancy obese. Pre-pregnancy obesity and excessive gestational weight gain increase miscarriage rates and obstetric and neonatal complications, which result in a lower healthy live birth rate. In addition to its negative consequences for the mother, obesity has been shown to be an important risk factor for chronic illnesses, such as cardiovascular disease, metabolic syndrome and type 2 diabetes in the adolescence and adulthood of the offspring. Moreover, maternal obesity causes psychological problems, physical disabilities and higher healthcare costs. Fetal programming of metabolic function induced by obesity, through physiological and/or epigenetic mechanisms, may have an intergenerational effect and could, thus, perpetuate obesity in the next generation. In order to break this vicious circle and avoid serious short- and long-term negative outcomes for both mothers and fetuses, the prevention and adequate management of obesity and gestational weight gain are essential.

Keywords

Birth outcomes, fetal programming, obesity, offspring, pregnancy

History

Received 15 January 2013
Revised 22 January 2013
Accepted 11 February 2013
Published online 20 March 2013

Introduction

Obesity, formally identified as a global epidemic by the World Health Organization (WHO) in 1997 [1], is one of the greatest health problems of the 21st century [1]. Body mass index (BMI) is calculated as weight in kilograms or pounds divided by height in squared meters or inches, rounded to one decimal place. According to WHO criteria [1], obesity is defined by three grades of severity: grade I obesity (30–34.9 kg/m^2), grade II or severe obesity (35–39.9 kg/m^2) and grade III or massive obesity (BMI $\geq$ 40 kg/m^2). Adult BMI increases very slowly with age, so age-independent cut-off points can be used to grade obesity. In children, however, classifying obesity during childhood or adolescence is further complicated by the fact that BMI varies substantially depending on the stage of growth and age. Obesity in children and adolescents aged 2–19 years is diagnosed when BMI is >95th percentile [2] and this definition includes not only the relationship between weight and height, but also between age and sex.

Weight excess is a recognized risk factor for chronic illnesses, most notably cardiovascular disease, metabolic syndrome and type 2 diabetes [3,4]. Its prevalence is increasing rapidly all over the world, especially in urban areas [1], in rich and poor countries and in all sectors of society, and is expected to continue to rise [5].

Obesity became increasingly prevalent in the United States during the last decades of the 20th century [6], and recent data show that more than one-third of adults and almost 17% of children and adolescents were obese in 2009–2010. Rates are similar in men and women and higher among older women than younger women, among adolescents than preschool-aged children, and in low educational levels [7]. The prevalence of obesity in Europe ranges from 4% to 28.3% in men and from 6.2% to 36.5% in women. Eastern Europe and the Mediterranean countries have higher rates than Western and Northern Europe [8]. In broad terms, it can be said that in the USA and many European countries 30% of women are obese and 6% are morbidly obese, according to the WHO criteria [1,5]. However, obesity is not just a problem of industrialized countries, as it is also becoming more prevalent in the developing world. For example, in the African continent, 5% of women are currently classed as obese and nearly a fifth of adults are predicted to be obese by 2030 [9].

Obesity affects all age groups, including childhood, adolescence and adulthood [10], and consequently represents an important medical risk factor to women who become pregnant, that are now more likely to enter pregnancy in an obese state. In fact, in Europe and the United States, 20–40% of pregnant women are obese or reach excessive weight gain in pregnancy [11]. Racial and ethnic factors also have an important bearing on maternal obesity and weight gain during pregnancy. A study among pregnant women who were not obese before pregnancy, found that African American women are more likely to gain weight in excess during pregnancy, white females are more likely to achieve their target weight, Hispanic women are least likely to achieve their target weight and Asian women are most likely to gain less than their recommend weight [12]. In a 10-year prospective study of women aged 18–30 years, black women were three times more likely to become obese than white women when age, parity, smoking, sociodemographics and other risk factors were controlled [12].

Although the behavioral patterns in question and their environmental determinants are complex, the obesity epidemic seems to be the result of an energy imbalance involving a reduction in physical activity, changes in dietary composition and

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Table 1. Short- and long-term complications associated with maternal obesity.

Maternal	Fetal/neonatal	Postnatal
• Miscarriage • Gestational nonproteinuric hypertension • Preeclampsia • GDM • Urinary infections • Preterm birth • Assisted vaginal delivery • Cesarean section • Wound infection/breakdown • Postpartum bleeding • Postpartum thromboembolism • Anesthetic complications • Longer hospitalization • Intrauterine fetal demise (stillbirth)	• Congenital anomalies: – NTDs – Omphalocele – Congenital heart disease • Fetal distress • Macrosomy (>4500 g) • Hydramnios • Shoulder dystocia • Hypoglucemia • Jaundice	• Obesity • Type 2 diabetes • Cardiovascular diseases • Osteoporosis • Cancer • Neurodevelopmental delay • Aging

high-calorie diet [13]. In addition, rising obesity rates are associated with food marketing [14], especially among children. However, there are additional factors that may explain the current prevalence of this health problem, such as genetic and epigenetic mechanisms, cultural norms, government policy, the environment, biological bases of food preferences and mechanisms that regulate motivation for physical activity [11–15].

The present paper reviews the impact of maternal obesity, not only on short-term consequences the offspring, but also on long-term consequences during childhood, adolescence and early adulthood, such as cardiovascular disease, metabolic syndrome, type 2 diabetes, osteoporosis, cancer, neurodevelopmental delay and ageing. To the best of our knowledge, there is no previously published review in the English medical literature that addresses all of the aforementioned health consequences.

Obesity-associated short-term (obstetric and neonatal) complications

Maternal obesity has been associated with obstetrical – in the three trimesters of pregnancy – and neonatal complications [16,17] (Table 1). Miscarriage rates and unexplained stillbirth are higher among obese women who have conceived naturally [18] or through Assisted Reproduction Techniques [17–19]. According to a meta-analysis of nine studies, obese women have an estimated risk of stillbirth twice of that of women of normal weight [20].

Obesity increases the risk of pregnancy-induced hypertension and preeclampsia (gestational proteinuric hypertension), with an odds ratio of between 2 and 3 [21]; a risk which rises linearly with BMI. For each 5–7 kg/m^2 increment in BMI, there is a corresponding two-fold increase in the risk of developing preeclampsia [22]. Maternal obesity is also associated with a higher probability of both pre-gestational diabetes and gestational diabetes mellitus (GDM) [23]. It has been reported that weight gain in the 5 years prior to becoming pregnant raises the risk of developing GDM, especially in the case of women who were not initially obese [23]. Insulin resistance increases progressively throughout pregnancy as a result of the continuous production of counter-regulatory hormones by the placenta. However, obese women have higher insulin resistance (lower insulin sensitivity) than women of normal weight, which results in elevated availability of lipids for fetal growth and development [24]. In fact, there is a higher expression of genes related to lipid metabolism and transport in the placenta of obese women with GDM, which results in a higher birth weight and fat mass in their offspring. More than 50% of women with GDM acquire diabetes within 20 years of delivery [25]. Offspring born of GDM pregnancies are more likely to develop macrosomia and shoulder dystocia, childhood obesity and type 2 diabetes mellitus [26].

Maternal obesity makes preterm labor, operative vaginal delivery and cesarean section more likely in both primigravid and multigravid women, and negatively affects the outcome of vaginal birth after cesarean [27]. The rate of cervical dilation in both nulliparous and multiparous women declines as maternal BMI rises [28], which shows that obese women are at a higher risk of experiencing dysfunctional labor. Moreover, obese pregnant women are also more likely to present intraoperative and postoperative complications (including postpartum hemorrhage), anesthetic complications (failed intubation at the time of general endotracheal anesthesia), postoperative wound infection and dehiscence, thromboembolism and endomyometritis in the puerperium [29]. Obesity is associated with 18% of obstetric causes of maternal mortality and 80% of anesthesia-related deaths [30].

Female obesity is also related to adverse fetal/neonatal outcome, such as macrosomia (defined as a birth weight >4.000 g or >95th percentile of gestational age) [31], which increases by 2–3-fold, shoulder dystocia, fetal distress, hypoglycemia, jaundice, stillbirth and congenital malformations (by 2–3 times), including heart, great vessels, ventral wall and intestine defects, hydrocephaly, omphalocele and neural tube defects (NTDs) [31], even after controlling for ethnicity, maternal age, education and socioeconomic status. These findings could be explained by the insufficient absorption or distribution of essential nutrients, such as folic acid, by chronic hypoxia, by incremented circulating levels of triglycerides, uric acid, estrogen and insulin, by hyperglycemia associated with insulin resistance and leading to GDM, or by poorer visualization of fetal organs by ultrasound, which can lead to subsequent errors in sonographic prenatal diagnosis [32,33].

In a large retrospective cohort study [34], including macrosomic neonates, it was demonstrated that the risk of obstetrical complications was three-fold higher in obese versus non-obese mothers (17% versus 6%). Data from mother–child pairs participating in the 2012 Project Viva [35] show that the lowest predicted prevalence of adverse obstetrical and neonatal outcomes occurred corresponded with a weight gain of 11.2 kg for women with normal weight and with a weight loss of 7.6 kg for obese women. Relatively small weight increments between pregnancies in the same women are also associated with adverse maternal outcomes, as shown in a cohort study in which health complications increased by 30–110% in mothers who gained more than three units of BMI between two consecutive pregnancies [36]. Collectively, these data underline the importance of adequate gestational weight gain in pregnant obese women, in order to avoid the aforementioned deleterious obstetric complications for

Table 2. Guidelines for pregnancy weight gain.

Pre-pregnancy weight	Recommended weight gain
Underweight (BMI <18.5)	28–40 lb (13–18 kg)
Normal weight (BMI 18.5–24.9)	25–35 lb (11–16 kg)
Overweight (BMI 25–29.9)	15–25 lb (7–11 kg)
Obese (BMI ≥30)	11–20 lb (5–9 kg)

BMI (kg/m^2).

both mother and fetus, which lead to a lower healthy live birth rate, in both natural and assisted conceptions [37], and higher economic costs (approximately five-times higher than the average) in the management of antenatal care [38].

To minimize the negative health consequences of obesity, a series of guidelines for pregnancy weight gain were published by the Institute of Medicine, in May 2009 [39], (Table 2). These guidelines established ranges of recommended weight gain for underweight (28–40 lb), normal-weight (25–35 lb), overweight (15–25 lb) and obese (11–20 lb) gravidas, depending on various factors, including pre-pregnancy BMI and maternal health [39]. In short, women should attempt to conceive at a normal weight if they wish for better obstetric outcomes, and a lower caloric diet can help to reach this goal during pregnancy without increasing the risk of low birth-weight.

Long-term consequences of maternal obesity on the offspring (fetal programming)

In addition to the previously cited complications, it is well documented that offspring born from obese women are more likely to develop health problems in their life, including obesity, type 2 diabetes, cardiovascular disease and cancer [1,6–13] (Table 1). In his 1990 paper entitled, ''*The fetal and infants origin of adult disease. The womb may be more important than the home*'' [40], David Barker emphasized the importance of the intrauterine environment rather than the environment in later childhood – including the home, diet and other influences [40]. According to the ''Barker hypothesis'' about the developmental origins of adult disease, conditions in the maternal womb have a programming effect on fetal physiology, a phenomenon called ''fetal programming'', by which if a fetus is deprived of an adequate supply of nutrients in the womb, it will be irrevocably ''programmed'' and predisposed to an increased risk of disease in adulthood. With this concept, termed as ''metabolic memory'', Barker emphasized developmental plasticity as an additional factor to the significant generational aspect of disease. Moreover, due to fetal programming, obesity can become a self-perpetuating problem. Daughters of obese women may themselves be vulnerable to becoming obese, as underlined by the words ''Your Mother's Mother: The Key to your Health'', the title of a lecture delivered by Barker in 2010 [41].

The concept of fetal programming has been supported by several studies. In a prospective cohort of 146 894 offspring, adult adiposity was associated with maternal weight and was shown to be influenced by intrauterine mechanisms in obese mothers [42]. In a longitudinal cohort study of 4168 infants, it was found that the prevalence of obesity at the age of 16 years among offspring of obese and GDM mothers was 40% and 26%, respectively. This prevalence persisted in offspring of the obese women but not among those of the GDM women [43], which points to maternal obesity being a risk factor for increased adiposity in the offspring at birth and into adulthood, either directly or through the metabolic complications it produces.

Maternal hypercholesterolemia is associated with increased fatty streak formation in human fetal arteries and accelerated progression of atherosclerosis during childhood [44]. In another report, offspring of diabetic rats exhibited an altered differentiation of hypothalamic neurons, which was avoided by normalizing the animals' glycemia levels and could have been due to an intrauterine diabetic environment [45] that increased the risk of obesity and diabetogenic status of offspring in adulthood.

All these data provided evidence of an *in utero programming* of metabolic syndrome in the offspring of obese women, highlighting a risk of disease that is already present before birth. It has long been recognized that newborns of obese and/or GDM women weigh more than those of women of normal weight and/or normal glucose tolerance, because of an increase in fat mass, that strongly correlates with a decreased maternal insulin sensitivity and a higher maternal pregravid BMI, respectively [46]. This enhanced adiposity at birth is also a risk factor for childhood obesity and long-term metabolic dysregulation [25]. It is well-established that obesity and insulin resistance are factors in the development of the metabolic syndrome in adults. Indeed, obese women begin their pregnancy more insulin resistant and more prone to β-cell dysfunction than their lean counterparts, which is largely due to adipose tissue dysregulation and is influenced by ethnicity and age [47]. Consequently, with the pregnancy-related progression of insulin resistance, obese women that are genetically predisposed have an elevated risk of developing type 2 diabetes.

A question that arises is whether, neonates of obese women, in addition to increased adiposity, have augmented insulin resistance and inflammatory markers at birth. Catalano et al. were the first to offer an answer to this question, reporting that the fetuses of obese women become insulin resistant *in utero*, as reflected by their umbilical cord glucose and insulin concentrations [48], thus supporting the concept of fetal programming. Data in rats have demonstrated that obesity contributes directly to the development of adiposity, adipose tissue dysfunction and metabolic disease later in life. In a study including 276 men and women [49], Reynolds et al. reported that the percentage body fat was higher in offspring of primiparous mothers with a higher pre-pregnancy BMI and demonstrated a relation between maternal parity and adiposity during adulthood among their offspring. Being a firstborn seems to be associated with elevated fat mass in both childhood and adolescence, probably due to a resetting of the leptin and glucocorticoid axis within the adipocyte, which contributes to increased adipogenesis during gestation and after birth [50].

One theory concerning how obesity and metabolic diseases can occur in offspring is related to epigenetic alterations of genes [51,52], which results in the transmission of DNA or RNA without altering the nucleotide sequence, induced by *in utero* environment through insulin resistance, inflammatory milieu and other hormonal factors. It has been found that neonatal offspring rats exposed to high fat diet show glucose intolerance because of increased gluconeogenesis and histone modification, which encodes the phosphoenolpyruvate carboxykinase 1 enzyme [53]. In line with these observations, developmental overfeeding in rats leads to an epigenetic malprogramming of the insulin receptor promoter. These data suggest that obese gravidas carry an environment that may impair the fetus epigenomic-associated metabolic status and consequently lead to disease into adulthood.

Based on the accumulated evidence, it is probable that birth weight, related to maternal obesity, as an indicator for genetic and environmental determinants during the intrauterine life, has a positive association with adult bone mass and may therefore have a bearing on the risk of osteoporosis later in life [54,55]. However, further studies are required to investigate the consistency of this risk in the offspring of obese women.

Barker et al. explored the association between pubertal growth of girls and prostate cancer in their sons and found a hazard ratio

of 2.2 (1.3–3.7; $p<0.001$) in men whose mothers weighed more than 80 kg in late pregnancy compared with those whose mothers weighed 60 kg or less [56]. Evidence shows that, under the influence of dietary nutrients, ''marked'' regions of DNA can become ''unmarked'' and that the estrogen receptor, mitogen-activated protein kinase, and tumor suppressors BRCA1, p53 and caveolin-1 are among the genes affected by diet-induced alterations in programming/reprogramming [57]. Thus, diet during pregnancy and puberty may play an important role in determining cancer risk in later life by inducing epigenetic changes that modify vulnerability to this disease.

Early life programming and transcriptional regulation in adulthood may also contribute to an increased risk of autism, developmental delay, deficits in expressive language and other neurodevelopmental impairments [58], as demonstrated in a recent study, in which obese mothers were found to be twice as likely to have a child with developmental delay and 1.7 times more likely to have a child with autism [59]. Moreover, high maternal BMI, especially in early pregnancy may lead to a predisposition to schizophrenia in the offspring, probably due to higher levels of second-trimester pro-inflammatory cytokines [60,61].

There is evidence linking accelerated aging processes and obesity, a state of increased oxidative stress and inflammation in the organism that affects telomeres, markers of biological aging rates that play a critical role in maintaining genomic integrity and are involved in age-related metabolic dysfunction [62].

According to a study that measured the length of telomeres in 1122 women aged 18–76, obesity may speed up the ageing process by 8.8 years by accelerating telomere erosion [63]. Experiments in mice suggest that obesity also increases the formation of reactive oxygen species in fat cells, ultimately resulting in the activation of the p53 tumor suppressor, inflammation and the promotion of insulin resistance [64]. There is growing evidence that maternal obesity leads to premature and unhealthy ageing, by causing early metabolic or genetic vulnerability, that begins with insulin resistance and leads to oxidative-stress, DNA damage and epigenetic changes. These processes vary with genetic and environmental factors, resulting in altered gene expression/repair, disease and pathological ageing [65–67].

It is also thought that maternal obesity is associated with metabolic disease on the offspring as a result of impaired placental function. Indeed, a prospective observational study in a non-human primate model detected increased placental inflammation and a reduction in uterine and placental blood flow, in mothers on a high-fat diet, factors that favour placental ischemia and stillbirth [68]. Moreover, a recent study has revealed for the first time that maternal obesity is associated with impaired iron transfer to the fetus, probably due to the effects of a chronic proinflammatory environment and increased levels of hepcidin [69].

This body of evidence highlights the mechanisms of action by which maternal nutrition can have an impact on offspring (Figure 1).

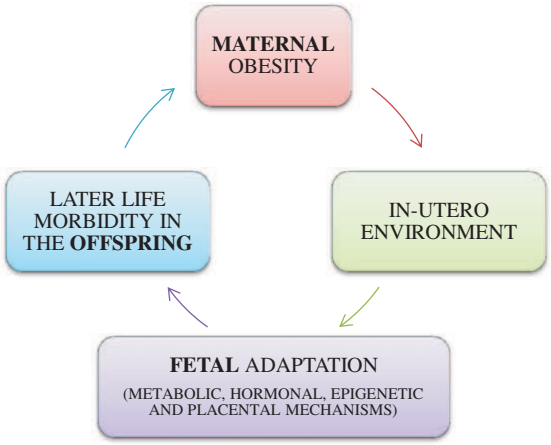

Figure 1. Fetal programming of adult diseases and intergenerational propagation of obesity. Stressors such as malnutrition, excess cortisol or hypoxia can alter gene expression in the embryo, thus predisposing the offspring to health problems in later life. Female offspring may give birth to offspring that are also programmed, therefore causing the cycle to be repeated in the next generation.

Conclusion

Maternal obesity constitutes a global health problem and is associated with adverse maternal and perinatal outcome. As discussed in this review, many studies in animal and human models have shown that female obesity during pregnancy is associated with programming of chronic diseases during the offspring's postnatal life, including cardiovascular disease, metabolic syndrome, type 2 diabetes, osteoporosis, cancer, neurodevelopmental delay and aging. Therefore, medical interventions, modifications of individual behavior or environmental changes, including dietary or exercise therapies, are needed to enhance periconceptional weight loss and to break the vicious circle of intergenerational obesity.

Likewise, the perinatal period of development should be the focus of future research about interventions that can reduce the lifelong effects of obesity on offspring health. Moreover, increased knowledge about programming towards obesity is essential if more effective preventive and therapeutic approaches are to be developed. In this context, large patient cohorts and long-term randomized controlled trials are necessary to provide a better understanding of the underlying genetic predispositions and mechanisms of maternal and fetoplacental interactions.

Obesity prevention is an important health priority and governments, international health organizations and society must collaborate to develop effective treatments in a coordinated approach [70].

Declaration of interest

The authors report no declarations of interest.

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