

Review

Obesity in pregnancy

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ABSTRACT

Obesity, the most common metabolic disorder, concerns, among others, women of reproductive age and, when it occurs before or during pregnancy, constitutes a major risk factor for both maternal and fetal complications. The complications of obesity in a prospective mother include subfertility, miscarriage, thrombo-embolism, hypertensive disorders, metabolic syndrome, preterm delivery and higher frequency of cesarean section. Fetal complications include intra-uterine death, congenital anomalies and macrosomia. Moreover, the complications of maternal obesity do not only involve the fetus; they also extend beyond fetal life into childhood and adulthood. The mother's diet during pregnancy creates a metabolic environment that affects fetal growth and may result in later development of metabolic syndrome and cardiovascular disease, a phenomenon known as "developmental origin of adult disease". Since the expectant mother is usually more motivated to accept lifestyle modifications, pregnancy is a period during which obesity can be more effectively managed. The control of body weight during this period is of paramount importance for pregnancy outcome as well as the health status of the mother and the neonate.

Keywords: Developmental origin of adult disease, Diet, Metabolic syndrome, Obesity, Physical exercise, Pregnancy

INTRODUCTION

The alarming increase in the prevalence of obesity worldwide, currently the commonest metabolic disease, has led the World Health Organization (WHO) to consider obesity as one of the most serious global health problems of the 21st century.¹ Obesity is defined as excessive body fat to an extent that is highly likely to impair health and increase morbidity and mortal-

ity. Body mass index (BMI) is the most frequently applied indicator of obesity. Thus, individuals with a BMI of 25 to 30 kg/m² are categorized as overweight, and those with a BMI over 30 kg/m² are considered obese. According to WHO, the prevalence of obesity in pregnancy ranges from 1.8 to 25.3%.¹ Obesity before and during pregnancy constitutes a major risk factor for both maternal and fetal complications,^{2,3} while it has been shown that offspring of obese women have a higher likelihood of becoming obese during childhood and of developing metabolic syndrome in adulthood (Figure 1).⁴ Pregnancy is a period during which obesity can be relatively effectively confronted

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Received 23-05-10, Revised 28-07-10, Accepted 15-08-10

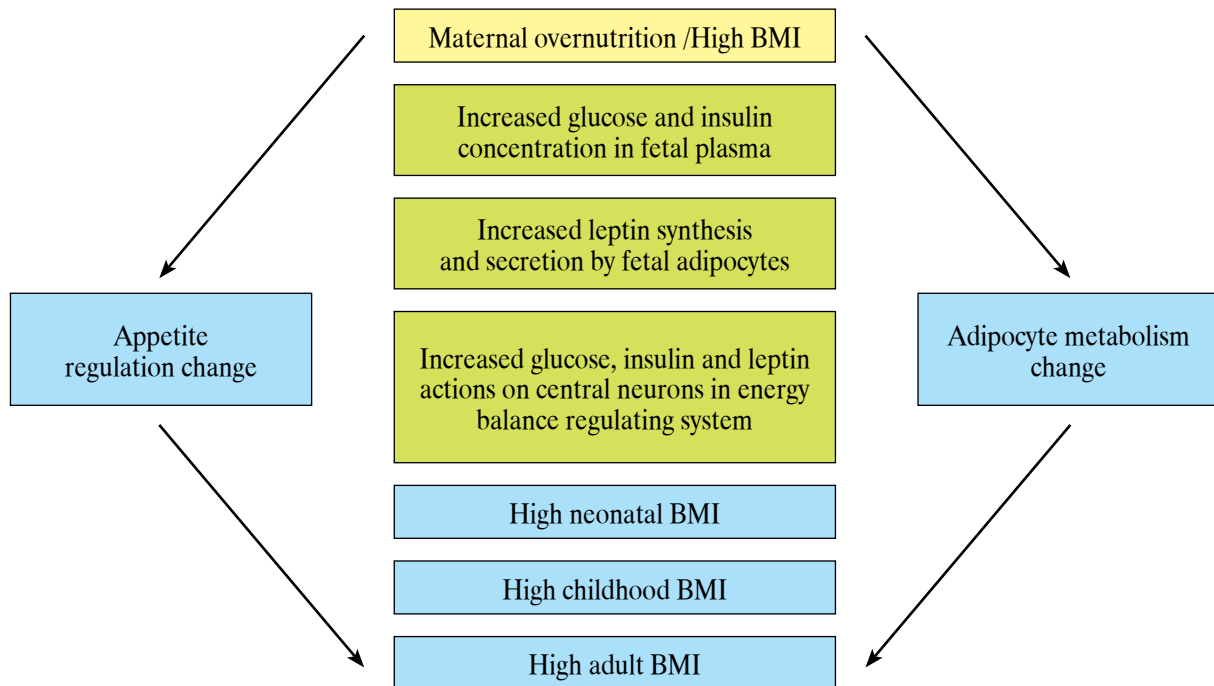


Figure 1. Possible relationships between maternal diet and fetal macrosomia. (From McMillen IC, et al, 2006⁴ with permission).

as the mother is more disposed to accept lifestyle modifications, such as balanced diet and physical exercise, which will most likely improve fetal health.² The control of body weight during this period is of paramount importance for delivery outcome as well as maternal and neonatal health. In the present communication, data on the effects of obesity prior to and during pregnancy on the health status of mother and fetus will be reviewed.

OBESITY BEFORE PREGNANCY

Obese, as well as underweight, women have reduced fertility as compared to women with normal body weight, this being observed in both natural conception⁵ and conception achieved by assisted reproduction techniques (ARTs).⁶ Subfertility observed in obese women is partly attributed to the decrease in frequency or complete absence of ovulation.^{2,3} The prevailing cause of oligo- or anovulation is polycystic ovary syndrome (PCOS), which is characterised by central visceral obesity in 40% of the cases.⁷ Moreover, in a wide context of metabolic disorders, low concentration of serum high-density lipoprotein (HDL) cholesterol, high concentration of triglycerides and

low-density lipoprotein (LDL) cholesterol^{8,9} as well as increased concentrations of plasminogen activator inhibitor-1 (PAI-1) tend to co-exist.^{10,11} All these metabolic derangements increase the risk of developing arterial hypertension, coronary heart disease and thrombosis. In addition, hyperinsulinemia promotes the production of testosterone and Δ_4 -androstendione from the theca cells in the ovary and results in a condition of hyperandrogenemic anovulation, with a phenotype characterized by hirsutism, obesity, acne, seborrhoea and hair loss.¹²

Obesity has been observed to exert a negative impact on ARTs.¹³ Specifically, obesity may adversely affect the duration of ovarian stimulation, number and quality of oocytes and embryos, fertilization rate, embryo transfer rate as well as implantation and pregnancy rates. In obese women, a longer duration of ovarian stimulation and higher doses of gonadotropins are required. Additionally, higher cancellation rates and higher incidence of follicular asynchrony are often observed.^{13,14} The lower number of oocytes retrieved in overweight and obese as compared to normal weight women may be due to the lower number of follicles, technical difficulties or both. Moreover, obesity can prevent proper trans-abdominal ultrasono-

graphic imaging during embryo transfer. All these mechanisms may be responsible for the decrease in implantation and pregnancy rates in obese women undergoing ART.¹⁵

OBESITY DURING PREGNANCY

A. Maternal complications

The recommended gestational weight gain is 11.5 to 16.0 kg, (0.5 to 2.0 kg for the first trimester and 0.35 to 0.50 kg per week for the second and third trimesters) (Table 1).¹⁶ It is strictly recommended for overweight and obese pregnant women to limit weight gain to a minimum and this aim is achieved by a balanced diet of high nutritional value, which results in both weight control and normal embryo growth. Women who are overweight before pregnancy are far more likely to exceed the weight gain recommendations during pregnancy and to experience greater risk of adverse complications,¹⁷ as outlined below.

Miscarriage

Although excess body weight has been correlated with increased risk for first-trimester miscarriage, the results of various studies are controversial and far from being conclusive.¹⁸⁻²⁰

Thrombo-embolism

Pregnancy *per se* constitutes a prothrombotic state characterized by an increase in the plasma concentration of coagulation factors I, VII, VIII and X, a decrease in protein S and inhibition of fibrinolysis.²¹ These changes in combination with other risk factors, such as advanced maternal age, high parity, cesarean section, pre-eclampsia and obesity, result in an increased risk for venous thrombosis. According

to several studies, obesity (BMI >30 kg/m²) doubles the risk of thrombosis by increasing the concentration of factors VIII and IX, but not of fibrinogen.²² Furthermore, BMI >25 kg/m² combined with oral contraceptive pills greatly increases²² the risk of thrombosis among women aged 15-45 years.

Gestational diabetes

Approximately 3-10% of women will be affected by gestational diabetes.³ Although many factors contribute to this, such as ethnic origin, age and family history, obesity constitutes an independent risk factor as the incidence of gestational diabetes is two- to three-fold higher in obese and overweight as compared to normal weight women.³ Moreover, obesity and diabetes play independent roles in determining fetal size. Women with gestational diabetes and normal body weight who control glycemia with diet, insulin or anti-diabetic drugs present an incidence of neonatal macrosomia comparable to that of women without diabetes.²³ In addition, insulin treatment prevented macrosomia in overweight and obese women. On the other hand, in obese women on diet who managed to control glycemia, as well as in overweight and obese women who failed to do so, irrespective of treatment, the incidence of macrosomia remained high.²³

Hypertensive disorders and metabolic syndrome

Obesity is associated with insulin resistance. Insulin resistance and consequent hyperinsulinemia can result in such conditions as hypertension, hyperlipidemia, degenerative heart disease, hyperuricemia and glucose intolerance or diabetes type 2. Hyperleptinemia, increased PAI-1 concentrations, micro- or macro-proteinuria and endothelium dysfunction have also been reported. This group of disorders has been collectively described as “metabolic syndrome”.

Table 1. Recommendations for total and rate of weight gain during pregnancy, according to pre-pregnancy body mass index. (From the Institute of Medicine and National Research Council, 2009). Re-examining the guidelines. Washington, DC: The National Academic Press.¹⁶

Pre-pregnancy BMI	Total weight gain (kg)	Rates of weight gain at second and third trimester (kg/week)
	Range	Mean (range)
Underweight: <18.5 kg/m ²	12.5 - 18.0	0.51 (0.44-0.58)
Normal weight: 18.5 - 24.9 kg/m ²	11.5 - 16.0	0.42 (0.35-0.50)
Overweight: 25.0 - 29.9 kg/m ²	7.0 - 11.5	0.28 (0.23-0.33)
Obese: ≥30.0 kg/m ²	5.0 - 9.0	0.22 (0.17-0.27)

Calculations assume a 0.5-2 kg weight gain in the first trimester.

During pregnancy, obese women face increased risk of developing hypertension, pre-eclampsia and gestational diabetes. Specifically, women with a BMI $>30 \text{ kg/m}^2$ have a two- to three-fold higher risk for developing pre-eclampsia, while this risk doubles for an increase in BMI prior to pregnancy by $5\text{-}7 \text{ kg/m}^2$.²⁴ Waist circumference is considered as the most sensitive index of visceral obesity, which is directly associated with an increased risk for hypertensive disorders. At the same time, waist circumference can identify up to 46% of the subjects who are liable to develop metabolic syndrome within the next five years.²⁵ On the other hand, obesity and a previous pregnancy complicated by pre-eclampsia constitute the main risk factors for developing severe pre-eclampsia in the current pregnancy. Pre-eclampsia is also associated with an increased risk for coronary heart disease in later life.²⁶

Preterm delivery

Current evidence indicates that obesity during pregnancy leads to induced preterm delivery but not spontaneous preterm birth, which is usually encountered in women with low BMI.^{27,28} Nevertheless, the data are still inconclusive.^{29,30}

Cesarean section

Studies suggest a two-fold³ increase in the risk for cesarean section in obese women even without additional risk factors. Cesarean section in this group is of great concern, as women who are overweight or obese are more susceptible to post-operative complications, such as excessive blood loss, deep venous thrombosis, wound infection and postpartum uterine infection.

Moreover, obesity has been associated with intra-partum complications and vaginal operative delivery.^{31,32}

Long-term complication

Obese women tend to retain gestational weight gain more frequently than women of normal body weight.^{17,33} It is also very important to note that women who developed gestational diabetes have a 50% likelihood of developing type 2 diabetes within the following ten years.³⁴

B. Fetal complications

Maternal obesity is associated with an increased

risk for perinatal mortality and occurrence of genetic disorders.³ The most common complications for the fetus are intrauterine death, genetic disorders and macrosomia. In the long term, large for gestational age (LGA) neonates of obese or diabetic mothers are prone to development of childhood obesity and metabolic syndrome in their adult life.³⁵

Fetal death

Fetal death constitutes a dramatic development of any pregnancy, especially when it takes place in late pregnancy. In some studies, an up to five-fold increase in intrauterine death as well as increased infant mortality rate has been recorded in obese women.³⁶ There also appears to be a correlation between maternal BMI and infant mortality rate.³⁷

Congenital anomalies

Prenatal screening for congenital anomalies becomes problematic in obese women due to difficulty of interpreting blood serum indices as well as inability to display the fetal anatomy on the ultrasonogram.³ These difficulties could, at least in part, explain the increased incidence of congenital anomalies in fetuses of obese women. Nevertheless, there are data supporting an actual association between maternal obesity and genetic disorders. Specifically, the fetuses of obese mothers have a higher risk of developing abnormalities of the neural tube, as for example spinal bifida, cardiovascular abnormalities, as well as abnormalities of the abdominal wall such as omphalocele. These abnormalities are more prevalent in offspring of women with type 2 diabetes and folic acid deficiency, disorders that often coexist with obesity. Finally, maternal obesity results in an increased admission rate of the offspring to the neonatal intensive care unit.^{3,38}

Macrosomia

The association between maternal obesity and fetal macrosomia has been established by many studies.³ Maternal weight and insulin resistance before pregnancy affect fetal growth, as is reflected in the birth weight.³⁹ Obesity and insulin resistance alter placental function which, during the last weeks of pregnancy, increases the availability of glucose, free fatty acids and aminoacids to the fetus.⁴⁰ Thus, maternal hyperglycemia induces fetal hyperglycemia

and, as a consequence, hypertrophy/hyperplasia of the fetal pancreas and hyperinsulinemia. Insulin has a direct effect on cell division that leads to macrosomia. Therefore, women with diabetes are at high risk of delivering macrosomic babies. Obese women even with normal glucose tolerance have a two-fold higher risk of giving birth to macrosomic babies since both conditions are independently correlated to macrosomia. Given that the incidence of obesity is approximately ten-fold that of gestational diabetes, it is evident that maternal lifestyle exerts a great influence on the incidence of fetal macrosomia. Once again, there seems to be a quantitative relationship between maternal BMI and the risk of delivering a macrosomic/LGA neonate.^{41,42} Macrosomia, as well as maternal height and weight, gestational age and number of prior deliveries, are considered reliable predictors of the risk of obstetrical events, such as shoulder dystocia and injury of the brachial plexus.³

Long-term complications

There is considerable evidence that the complications of maternal obesity extend beyond intrauterine and neonatal life into childhood and adulthood, thus leading to serious life long health problems.^{43,44} Maternal obesity constitutes a risk for childhood obesity,⁴⁵ irrespective of birth weight and of smoking during pregnancy, as well as a risk for the appearance of the metabolic syndrome and cardiovascular disease in adulthood.

There is a large number of pathophysiologic mechanisms that could explain the fact that obese mothers give birth to obese children. Genetic factors are undoubtedly responsible to a certain degree for the tendency of both mother and child to be overweight. Additionally, the impact of the environment is to be taken into account since mother and child typically share the same eating habits.⁴ Moreover, the increase in food intake during pregnancy has a quantitative effect on the fetus, promoting the development of adipose tissue.⁴³

Childhood and adolescent obesity exerts a long-lasting physical and psychological impact and increases population morbidity and mortality. The increasing prevalence of maternal obesity before and during pregnancy results in a vicious circle of obesity in subsequent generations. Thus, obese mothers give

birth to obese daughters, who have a higher risk of suffering from obesity and diabetes during their own pregnancies.^{4,40}

Developmental origin of adult disease

The abnormal development of the fetus results in increased morbidity during childhood, adolescence and adulthood, a phenomenon known as “fetal programming” or “developmental origin of adult disease”.⁴⁶ The fetal adjustment to the uterine environment leads to permanent changes in the phenotype (i.e. physical structure, physiology and metabolism) which might not be fully functional in extra-uterine conditions. In order to explain this phenomenon, particularly the connection between fetal development and type 2 diabetes, the hypothesis of the “thrifty phenotype” was formulated. According to this, poor nutrition during intrauterine life, as reflected in low birth weight, results in adverse physiological or morphological characteristics (“developmental plasticity”) in certain organs (e.g. pancreas), while it respects others (e.g. brain). When the individual faces environmental changes in postnatal life, such as an increase in calorie intake, these adaptive changes are no longer favorable and lead to disease.³⁵ In addition to type 2 diabetes, the “thrifty phenotype” hypothesis possibly accounts for such diseases as hypertension, hyperlipidemia, atherosclerosis, cardiovascular disease and stroke, their common denominator being insulin resistance.⁴⁷

MANAGEMENT

Before pregnancy

Obtaining normal weight before pregnancy is an ideal goal since it is of paramount importance not only for conception but also for the outcome of pregnancy.¹⁶ However, many pregnancies are not planned and, even when they are, very few women consult a specialist on how to lose weight, the main reason being that the majority of women are reluctant to postpone their family planning in order to achieve the target weight. Nevertheless, it is now an established fact that weight loss before pregnancy results in a better chance for conception and increases the percentage of live births for obese women with or without PCOS.²

Treatment of obesity before pregnancy is a difficult

task. It is essential, however, that obese women are fully informed about the risks of obesity and the benefits of weight loss. Management includes improved lifestyle by balanced diet and physical exercise. Medical treatment and bariatric surgery can be considered as second-line options. A low-calorie diet with reduced glycemic load and an adequate amount of proteins and mono-unsaturated fats reduces hyperinsulinemia in six months.⁴⁸ Physical exercise, especially aerobic, results in weight loss as well as in the reduction of serum testosterone,⁴⁸ while anti-diabetic drugs, such as glibenclamide and metformin, might prove to be beneficial and have not proven harmful. Finally, bariatric surgery provides more permanent solutions in the event that the above-mentioned measures have failed.^{2,48}

During pregnancy

Given the fact that obesity or excessive weight gain during pregnancy constitute important risk factors for the mother and the fetus and, moreover, that women who gain excessive weight during pregnancy have a three-fold higher risk of becoming overweight in subsequent pregnancy,¹⁷ balanced diet and physical exercise during, and if possible before pregnancy are strongly recommended. Social trends which support the view that a pregnant woman should “eat for two” are not scientifically proven. On the other hand, it is essential that pregnant women follow a diet of high nutritional value which includes all food groups, whereas consumption of foods with high fat content and high glycemic index should be kept to a minimum. At the same time, provided that there are no medical or obstetric contra-indications, aerobic exercise of medium intensity has marked beneficial effects.² Thus pregnant women are counseled to exercise on a daily basis at a moderate degree (i.e. walking, swimming, aerobics) for 30 or more minutes.⁴⁹ Nevertheless activities that present a high risk of falls or abdominal injury as well as intense exercise must be avoided. Furthermore, given that exercise reduces the risk of developing pre-eclampsia, glucose intolerance and gestational diabetes, overweight and obese women should be encouraged to abandon sedentary lifestyle. Pregnancy is also the ideal time for other changes in lifestyle, such as quitting smoking and giving up other harmful habits. The mother should be encouraged and motivated to consider this effort as both an

investment in the maintenance of her own health as well as in that of her baby.⁵⁰

After pregnancy

The postpartum period is another suitable time for the mother to adopt healthy lifestyle habits that will allow her not only to lose the excessive weight gained during pregnancy but also to achieve ideal body weight in view of a prospective pregnancy. However, the need to care for the newborn baby, the psychological alterations of the puerperal period and previous failed attempts to lose weight often discourage women from making a serious effort. Thus, the support of the whole family and consultation with a dietician are required in order for the woman to combine healthy diet with physical exercise. While nursing is theoretically thought to facilitate postpartum weight loss, the results of relevant studies do not support such conclusions.^{51,52}

Healthcare providers have the potential to prevent high postpartum weight retention and future obesity by monitoring weight gain during pregnancy and giving appropriate advice about recommended amounts of gestational weight gain. Although there has been a substantial improvement in the management of maternal obesity over the last three years, more work is needed specifically concerning psychosocial issues and the public health aspects of maternal obesity.⁵³ To meet the needs of obese pregnant women, maternity services should consider close observation not only of the period of pregnancy but of the postnatal period as well through improving communication between hospital and public health services and developing services that will encourage pregnant women to optimally address all health concerns surrounding their obesity.

CONCLUSIONS

Maternal obesity constitutes a serious health risk for both mother and fetus, the impact of which increases with the degree of obesity. A non-balanced diet during pregnancy contributes not only to abnormal fetal development and subsequently increased neonatal morbidity and mortality but also to increased morbidity during childhood, adolescence and adulthood (“developmental origins of adult disease”). A systematic effort for weight reduction is imperative in

order to avoid transmitting obesity from generation to generation. Achieving this goal will most likely result in a sharp decrease in fetal and neonatal morbidity and mortality and will improve the outcome of offspring and of future pregnancies.

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