**UNIVERSITY OF DIYALA**
**COLLEGE OF MEDICINE**

# THE EFFECT OF OBESITY AMONG DM AND NON DM PREGNANT WOMEN

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## ABSTRACT

Women bear the predominant burden of our obesogenic environment, with a higher incidence of obesity than men, more impact on their fertility and success with treatment, and significant maternal and perinatal morbidity and mortality.In addition, gestational diabetes mellitus (GDM) is the most common medical complication of pregnancy, which increasing worldwide. It is associated with maternal and neonatal adverse outcomes. Maintaining adequate blood glucose levels in GDM reduces morbidity for both mother and baby. There is a lack of uniform strategies for screening and diagnosing GDM globally.

Maternal obesity is linked with adverse outcomes for mothers and babies. To get an overview of risk related to obesity in pregnant women, therefore our review and analysis of the 24 reviews was conducted. For inclusion, reviews had to compare pregnant women of healthy weight with women with obesity in many studies , and measure a health outcome for mother and/or baby. The review study showed gestational diabetes, pre-eclampsia, gestational hypertension, depression, instrumental and caesarean birth, and surgical site infection to be more likely to occur in pregnant women with obesity compared to women with a healthy weight. Maternal obesity is also linked to greater risk of preterm birth, large-for-gestational-age babies, fetal defects, congenital anomalies, and perinatal death. Furthermore breastfeeding initiation rates are lower and there is greater risk of early breastfeeding cessation in women with obesity compared with healthy

weight women. These adverse outcomes may result in longer duration of hospital stay, with concomitant resource implications. It is crucial to reduce the burden of adverse maternal and fetal/child outcomes caused by maternal obesity.
Women with obesity need support to lose weight particularly by regular exercise and diet before they conceive, and to minimise their weight gain in pregnancy.

***Keywords****:* Gestational Diabetes Mellitus(GDM, Blood glucose level, Exercise, Obesity, Overweight, Pregnant women

**CONTENTS**

# THE EFFECT OF OBESITY AMONG DM AND NON DM PREGNANT WOMEN

**LIST OF SYMBOLS AND ABBREVIATIONS**

| Symbol | Description |
|---|---|
| BTH | Baquba Teaching Hospital |
| BMI | Body Mass Index |
| WHO | World Health Organization |
| AOR | Adjusted odds ratio |
| CS | Caesarean section |
| GDM | Gestational diabetes mellitus |
| GPCC | Centre for Person-Centred Care, University of Gothenburg |
| NTD | Neural tube defect |
| OR | Odds ratio |
| PICOS framework used: | Population, intervention, comparison, outcomes and study designs |
| RCT | Randomised controlled trial |
| RR | Risk ratio |
| SSI | Surgical site infection |
| UK | United Kingdom |
| US | United States |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BCAA | Branched-chain amino acid |
| CETP | Cholesteryl ester transferase protein |
| FDR | False discovery rate |
| GDM | Gestational diabetes mellitus |
| gGT γ- | Glutamyl transferase |
| GlycA | Glycoprotein acetyls |
| HAPO | Hyperglycemia and Adverse Pregnancy Outcome |
| HOMA2-%B | Updated HOMA of steady-state beta cell function |
| HOMA2 | IR Updated HOMA of insulin resistance |
| HOMA2-%S | Updated HOMA of insulin sensitivity |
| hPL | Human placental lactogen |
| hsCRP | High-sensitivity C-reactive protein |
| IADPSG | International Association of Diabetes and Pregnancy Study Groups |
| LGA | Large for gestational age |
| SHBG | Sex hormone binding globulin |
| TCA | Tricarboxylic acid |
| tPA | Tissue plasminogen activator |
| UPBEAT | UK Pregnancies Better Eating and Activity Trial |

# CHAPTER 1

## INTRODUCTION & GENERAL INFORMATION

For more than a century, it has been known that diabetes antedating pregnancy can have severe adverse effects on fetal and neonatal outcomes . As early as in the 1940s, it was recognized that women who developed diabetes years after pregnancy had experienced abnormally high fetal and neonatal mortality. By the 1950s the term "gestational diabetes" was applied to what was thought to be a transient condition that affected fetal outcomes adversely, then abated after delivery. In the 1960s, O'Sullivan found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy. He proposed criteria for the interpretation of oral glucose tolerance tests (OGTTs) during pregnancy that were fundamentally statistical, establishing cut-off values approximately 2 standard deviations for diagnosing glucose intolerance during pregnancy .

In the 1980s those cut-off points were adapted to modern methods for measuring glucose and applied to the modern definition of gestational diabetes, glucose intolerance with onset or first recognition during pregnancy. While based on O'Sullivan's values for predicting diabetes after pregnancy, the diagnosis of gestational diabetes mellitus (GDM) also identifies pregnancies at increased risk for perinatal morbidity and long-term obesity and glucose intolerance in offspring. **(1)**

**-Population perspective**

Studies referred that, Clinical detection of GDM was carried out to identify pregnancies at increased risk for perinatal morbidity and mortality. Available data did not identify a threshold of maternal glycemia at which such risk begins or increases rapidly. A multinational study, the Hyperglycemia and Adverse Pregnancy Outcome study, is underway to explore this issue in a large multiethnic cohort. In the absence of a defined glucose threshold for perinatal risk, many different sets of glycemic criteria have been proposed and are employed worldwide for the diagnosis of GDM. The criteria currently recommended by the American Diabetes Association are based on O'Sullivan's criteria . The detection of GDM, a condition that is generally asymptomatic, involves screening in 2 sequential steps, followed by administration of a 2- or 3-hour OGTT to women

determined to be at risk by screening. Women with very high clinical risk characteristics may be diagnosed with probable pregestational (preexisting) diabetes based on the criteria provided. When the diagnostic criteria for a 3-hour OGTT presented in was applied to a group of Caucasian women in Toronto, approximately 7% had GDM . The frequency of GDM may vary among ethnic groups (higher in groups with increased prevalence of hyperglycemia) and with the use of different diagnostic criteria (higher when lower glucose thresholds are applied and vice versa) . Nonetheless, all approaches to GDM detection pinpoint and thereby allow diagnosis of women with glucose tolerance in the upper end of the population distribution during pregnancy.
A small minority of those women have glucose levels that would be diagnostic of diabetes outside of pregnancy . The great majority have lower glucose levels. Both groups impart to their offspring an increased risk of perinatal morbidity and long-term obesity and diabetes that appear to be related at least in part to fetal over nutrition in utero. **(1)**

Obesity and being overweight are becoming epidemic, and indeed, the proportion of such women of reproductive age has increased in recent times. Being overweight or obese prior to pregnancy is a risk factor for gestational diabetes mellitus, and increases the risk of adverse pregnancy outcome for both mothers and their offspring. Furthermore, the combination of gestational diabetes mellitus with obesity/overweight status may increase the risk of adverse pregnancy outcome attributable to either factor alone. Regular exercise has the potential to reduce the risk of developing gestational diabetes mellitus and can be used during pregnancy; however, its efficacy remain controversial. At present, most exercise training interventions are implemented on Caucasian women and in the second trimester, and there is a paucity of studies focusing on overweight/obese pregnant women . **(2)**
The global epidemics of overweight and obesity are leading health burdens worldwide; moreover, the proportion of overweight and obese women of reproductive age is increasing. Overweight and obesity are widely accepted to affect the entire pregnancy process and to constitute major risk factors for perinatal complications, such as gestational diabetes mellitus (GDM),hypertensive syndrome, fetal growth disorders, cesarean delivery, postoperative complications, wound infections, and deep vein thrombosis. Among them, GDM is a particular concern because of its own effects on other adverse

pregnancy outcomes, such as preeclampsia, macrosomia, or cesarean delivery. Our previous study showed that overweight and obese pregnant women have a >2-fold increased risk of developing GDM compared with nonobese women**. (2)**

Overweight and obesity pose a big challenge to pregnancy as they are associated with adverse maternal and perinatal outcome. Evidence of lifestyle intervention resulting in improved pregnancy outcome is conflicting. Hence the aim of the present study was to review and estimate the global and country-level burden of overweight and obesity among pregnant women and study the causes, consequences, and solutions regarding the obesity pandemic, the mechanisms of the effect of obesity on the female and male, the epigenetic consequences of male obesity, the marked effects on perinatal outcomes, and the effects of weight loss before conception and during pregnancy are exploring. Lifestyle modifications, in particular a healthy diet and exercise during the 3–6 months before conception and during treatment, should result in better outcomes than requiring weight loss before fertility treatments. Such fundamental changes toward a healthier lifestyle will achieve steady and sustainable weight loss and long-term benefits for general health. The role of bariatric surgery before pregnancy requires careful consideration

## CHAPTER 2

## LITERATURE REVIEW

Given the role of gut microbiota in regulating metabolism, probiotics administered during pregnancy might prevent gestational diabetes mellitus (GDM). This question has not previously been studied in high-risk overweight and obese pregnant women. Researches referees to determine whether probiotics (Lactobacillus rhamnosus and Bifidobacterium animalis subspecies lactis) administered from the second trimester in overweight and obese women prevent GDM as assessed by an oral glucose tolerance test (OGTT) at 28 weeks' gestation. Secondary outcomes included maternal and neonatal complications, maternal blood pressure and BMI, and infant body composition. **(3)**

The scientists reviewing and observed that women assume the predominant burden of our obesogenic environment. Obesity is more common in women than in men, has a greater effect on their spontaneous and assisted conception rates, and increases miscarriage, premature labor, stillbirth, perinatal risks such as gestational diabetes and hypertension, need for operative delivery, and other complications such as wound infection and thromboembolism. From a societal viewpoint, because of these medical issues and because obese women survive longer than obese men, they are responsible for well over three quarters of the extra direct health care costs due to obesity and over three-fold that of men. The Milken Institute calculated the direct health care costs of obesity for 2014 in the U.S. at $427 billion. Together with indirect costs, such as lost productivity, the yearly cost to the U.S. economy was a staggering $1.4 trillion—more than twice what the United States spends on defense and 8.2% of the entire U.S. gross domestic product. In the review on the causes, solutions, and general health risks of obesity, we point out that 38% of adult women in the United States are obese (vs. 34% of adult men), at least in part because of their smaller size relative to the onslaught of calories in our obesogenic environment and the cumulative

effect of extra weight gain with each pregnancy. Difficulty breast feeding, in part because of prematurity and operative delivery, also removes an important way that women can lose that extra weight postpartum. In addition to employer prejudice because of time off for pregnancy and child care, obese women also face the well documented reluctance to hire an obese person. Taken together, the total financial cost to the obese woman is large. We detail the many causes of obesity, including our success in providing inexpensive, calorie-dense foods, devices that reduce or eliminate physical exertion, and cheap, nonphysical entertainment. The extensive health consequences are enumerated, also the gut microbiome can be disrupted by an unhealthy diet, resulting in increased absorption of calories and systemic endocrine changes promoting appetite. Kelle Moley and her coauthor have contributed a detailed review of the complex mechanisms whereby obesity reduces female fertility. Notably, oxidative stress, inflammation, and insulin resistance are common mediators of those effects. Obesity is also a prominent aggravating factor in the development of polycystic ovarian syndrome (PCOS). Hyperandrogenism and insulin resistance in women with PCOS have been reported to be associated with a reduced basal metabolic rate, further promoting weight gain.. **(4)**

Obesity is a growing public health hazard worldwide. The proportion of global adult women with overweight increased from 29.8% (29.3±30.2%) in 1980 to 38.0% (37.5±38.5%) in 2013,and the increasing trend was observed in both high income and middle income countries.

Among pregnant women, increased body mass index (BMI) was associated with numerous pregnancy related complications, including gestational diabetes mellitus (GDM), pregnancy hypertension and preeclampsia .Women with overweight or obesity involved a relatively high risk of severe maternal morbidity and mortality. Previous experts reported a odds ratio (OR) for severe maternal morbidity of 1.1 for women with obesity class 1 (BMI 30.0±34.9) compared with women with normal weight (BMI 18.5±24.9). The OR for obesity class 2 (BMI 35.0±39.8) was 1.2, and for obesity class 3 (BMI _40) was 1.4 . Maternal obesity also increased perinatal mortality. A previous cohort study found that maternal obesity was associated with nearly 25% of stillbirth that occurred between 37 and

42 weeks' gestation . In addition, overweight and obesity were associated with elevated risks of fetal macrosomia, some birth defects, and metabolic disease of children . Considering the effect of pregnancy overweight and obesity on mothers and infants, it is need to investigate the burden of overweight and obesity among pregnant women. Thirty-two percent of Swedish pregnant women were overweight or obese in 2008±2010. The prevalence of overweight among pregnant women in Iceland increased form 25.9% to 27.7% within nine years . According to a retrospective cohort study in Canada, twenty-two percent of pregnant women were obese and 24% were overweight in 2004±2014. A recent meta analysis reported that the prevalence of maternal obesity in Africa ranged from 6.5% to 50.7% . However, previous studies exploring the prevalence of overweight and obesity among pregnant women were limited by the focus on a single country. The global burden of overweight and obesity among pregnant women remained unclear. Many previous studies explored obesity of pregnant women and its determinants. For low income women, fast food intake can increase caloric supply, which is sufficient to explain the increase of BMI in pregnant women . Compared with metropolitan residents, rural residents were more likely to be overweight and obese in many countries, such as the United States of America and China . However, countries with high rates of urbanization usually have higher rates of obesity than those with low rates of urbanization. A previous system review found a consistent positive association between urbanization and obesity in many countries in Southeast Asia, and the association was greater in low gross national income (GNI) countries . Experts argued that urbanization could tip the balance between energy intake and energy expenditure, namely decreases in physical activity and increases in the consumption of cheap fast food. Urbanization is usually accompanied by the transformation of industrial structure. In middle income and low income countries, a growing number of female work in service sectors. Occupational physical activity is an important determinant of daily energy expenditure. A previous study found that women in the sedentary occupation group had a higher risk of obesity compared to those in the agricultural occupation group if they had no education **.(5)**

Although the World Health Organization (WHO) and the Global Burden of Disease study (GBD) provided data of obesity and overweight data among adults, those data has not been fully used to explore the prevalence of obesity and overweight among pregnant women. It is needed to explore more evidence about overweight and obesity among pregnant women..**(5)**

Maternal obesity is becoming an increasing public health issue, and it is known that nutrition and metabolism play a crucial role in the health and wellbeing of both mother and fetus . Maternal obesity is reaching epidemic proportions, particularly in the United States (US), where prevalence of obesity in women aged 20-39 years increased from 28.4% in 1999 to 34% in 2008 but has now fallen slightly to 31.9%. Across Europe, similar increases from lower starting levels are seen. The latest European Perinatal Health Report showed that the lowest levels of overweight or obesity in pregnant women were in Poland (25.6%), France (27.2%), and Slovenia (27.8%). The majority of other European countries had rates of 30-37%, and Scotland had a prevalence of 48.4%, with 20.7% of all pregnant women in the range of obesity (5).

Maternal obesity is linked with increased rates of caesarean section, depression and medical complications . Babies of women with obesity also suffer from pre-term birth, still-birth and fetal anomalies. Maternal obesity is the most significant factor leading to obesity in offspring and, coupled with excess weight gain in pregnancy, also results in long-term obesity for women .

Several systematic reviews have been conducted in an attempt to synthesise an overall conclusion as to which outcomes can, with certainty, be linked with obesity in pregnancy. These reviews are of differing scope and quality and may, also, have opposing results, leading to confusion among clinicians as to what are the true risks related to maternal obesity. In addition, clinicians (and researchers) may read only one of a number of reviews and base clinical decisions or suggestions for changed practice on this, or ignore the evidence if the review is small, or does not cover their country. The benefit of bringing together a number of systematic reviews on a particular outcome is that the reader is more likely to be convinced by the weight of evidence. **(6)**

Obesity has been designated as one of the most important global health threats worldwide, and its prevalence has been increasing among women of reproductive age. Pregnant women constitute an important subpopulation with an elevated risk of obesity due to excessive weight gain. **(7)**

It has been shown that maternal obesity and excessive gestational weight gain (GWG) are associated with adverse obstetric and neonatal outcomes including spontaneous abortion, gestational diabetes mellitus (GDM), cesarean delivery, preeclampsia, neonatal macrosomia, and operative and anesthetic complications.

To support optimal pregnancy outcomes, the World Health Organization (WHO) recommended that the Institute of Medicine (IOM) develop guidelines for weight gain during pregnancy. However, the IOM recommendations on gestational weight gain are based on pre-pregnancy BMI without taking into consideration different race/ethnicity, age, or existing pregnancy complications. Women with GDM are at increased risk of maternal and fetal complications including preeclampsia, preterm birth, caesarean section and delivery of large for gestational age (LGA) infants. As obesity and GDM are frequently comorbid conditions, obesity and excessive gestational weight gain may compound these risks in GDM. Because fat is an endocrine organ and interacts with
diabetes, it is possible that the increased accumulation of fat has a differential effect on perinatal outcomes for women with GDM .**(7)**

Another study identify the independent and combined effects of age, BMI at first prenatal visit and GWG on the risk of GDM.

Older maternal age and being overweight/ obese were significantly associated with risk of GDM. Overweight/obese women with age ≥35 years had 2.45 times higher risk of GDM and having excessive GWG at second trimester further increased the risk of GDM. Age and BMI are independent risk factors for GDM but not GWG in the first and second trimester. The findings emphasize the need to focus on a healthy BMI before pregnancy and optimal GWG during pregnancy to improve pregnancy outcomes. **(8)**

Studies on the associations between pre-pregnancy BMI and GWG with risk of GDM showed that pre-pregnancy obesity and excessive GWG are independent

risk factors for the development of GDM. While overweight or obese women had an increased risk of GDM compared to lean or normal-weight women, excessive GWG, particularly between early and mid-pregnancy, was postively associated with risk of GDM**.(8)**

Other studies explained that, pregnancy is associated with insulin resistance (IR) and hyperinsulinemia that may predispose some women to develop diabetes. Gestational diabetes has been defined as any degree of glucose intolerance with an onset, or first recognition during pregnancy.This definition does not exclude the possibility that unrecognized glucose intolerance may have antedated the pregnancy, and so, the term hyperglycemia in pregnancy emerges to be more appropriate as suggested lately by the Endocrine Society.The International Association of Diabetes and Pregnancy Study Groups (IADPSG) classify hyperglycemia first detected during pregnancy as either 'overt diabetes' or 'gestational diabetes mellitus (GDM)'.3 In 2013, the World Health Organization (WHO) recommended that hyperglycemia first detected during pregnancy be classified as either 'diabetes mellitus (DM) in pregnancy' or 'GDM'.The prevalence of GDM varies from 1-20%, and is rising worldwide, parallel to the increment in the prevalence of obesity and type 2 diabetes mellitus (T2DM).The amount of GDM varies in direct proportion to the prevalence of T2DM in a given population, or ethnic group. The prevalence rates for GDM are higher for African, Hispanic, Indian, and Asian women than for Caucasian women. Recently, the prevalence of GDM has increased by 2-3 folds, ranging from 8.9-53.4%. This is mainly due to the adoption of the new criteria proposed by the IADPSG on screening, and diagnosis of GDM. The IADPSG recommends universal screening for GDM, and requires one single glucose value above the cut-off value during the oral glucose tolerance test (OGTT) for diagnosis. This dramatic rise in the GDM prevalence will have a major impact on health care systems. Also, the consequences of labeling a large number of women with GDM are not known. The GDM is associated with adverse maternal and neonatal sequelae. In a Hyperglycemia and Adverse Pregnancy Outcomes Study (HAPO), a large-scale (25,000 pregnant women) multinational epidemiologic study found significant associations between adverse pregnancy outcomes, and higher levels of maternal

glucose with no defined levels, after which the risk increases. Furthermore, the Australian Carbohydrate Intolerance Study (ACHOIS) in pregnant women, and the US multicenter randomized trial of treatment for mild gestational diabetes studies indicated that maternal hyperglycemia that does not meet diagnostic criteria for overt diabetes still has a correlation with perinatal disorders and problems. This association suggests a need to re-evaluate the standard criteria for diagnosing, and treating hyperglycemia in pregnancy, and welcome the new criteria. (**9)**

***Course of insulin sensitivity during pregnancy***. In early pregnancy, insulin secretion increases, while insulin sensitivity is unchanged, decreased, or may even increase. At mid pregnancy, insulin sensitivity starts to decline progressively, and became worse during the rest of the pregnancy, being worst in the late third trimester. It rebounds with the delivery of the placenta. Therefore, GDM usually develops in the late second trimester and disappears, instantly, post delivery.

***Risk factors for GDM***. Several risk factors are associated with the development of GDM. The most common risk factors are; obesity, older maternal age, past history of GDM, strong family history of diabetes, member of an ethnic group with a high prevalence of T2DM, polycystic ovary syndrome, and persistent glucosuria. A history of delivering big baby (birth weight ≥4000 g), history of recurrent abortions, and history of unexplained stillbirths, and history of essential hypertension, or pregnancy-related hypertension are other risk factors for GDM.

***Risks of GDM***. Women with GDM have an increased incidence of hypertensive disorders during pregnancy, including gestational hypertension, pre-eclampsia, and eclampsia. There is an increase risk of polyhydramnios that may increase the risk of preterm labor. Excessive fetal growth remains an important perinatal concern in GDM. Consequences of excessive fetal growth include birth trauma, maternal morbidity from cesarean deliveries, shoulder dystocia, and neonatal hypoglycemia. Other neonatal morbidities that potentially occur more frequently in infants of women with GDM include hyperbilirubinemia, hypocalcemia, erythema, and respiratory distress syndrome. Long-term complications of GDM

include diabetes and cardiovascular disease in the mothers, and obesity and diabetes in the offspring. Congenital anomalies do not occur at an increased rate in patients with gestational diabetes, as GDM usually occurs at the late second trimester when embryogenesis is completed **.(9)**

*Management of GDM.* The cornerstone of GDM management is glycemic control. The initial treatment for GDM is lifestyle interventions, which include medical nutrition therapy and daily exercise. Patients are required to check their glucose level frequently at home to assure that the glycemic targets are achieved. If the glycemic goals are not accomplished with these measurements, medical therapy should be initiated.**(9)**

***Blood glucose monitoring***. Women are instructed to carry out self monitoring of blood glucose (SMBG) 4 times a day, fasting glucose (upon awakening), and one or 2 hour post-meals (after the first bite of a meal). In GDM, monitoring of blood glucose after meals is preferred over pre-meal testing as the risk of macrosomia increases with increased maternal glucose levels post-meals. This was illustrated in a randomized clinical trial, which compared preprandial glucose monitoring to one hour post-prandial (PP) testing, and found macrosomia, cesarean deliveries, and neonatal hypoglycemia were significantly less frequent in women who monitor their glucose post-meals. However, it is not known whether a one hour, or 2-hour PP testing is the ideal goal for the prevention of fetal risks. Therefore, patients can monitor their glucose levels at one or 2 hours post-meal, whatever is convenient, or at the estimated peak blood glucose is most likely to occur post prandial, for example, choosing the time at which glucose was elevated during OGTT.**(9)**

***Medical nutritional therapy***. Medical nutritional therapy is the keystone of treating GDM as it maintains desired glycemic goals in 80-90% of GDM women. The optimal dietary prescription would be a diet that provides adequate nutrition to support fetal and maternal well-being, while maintaining normoglycemia with absence of ketones, and achieving appropriate weight gain in pregnancy. Caloric allowance could be calculated based on ideal body weight: 30 kcal/kg for women with a BMI of 22-25; 24 kcal/kg for women with a BMI of 26-29; and 12-15 kcal/kg for women with a BMI above 30. The carbohydrate intake should be reduced to 35-45% of the total calories, and distributed over 3 meals, and 2-4 snacks including bedtime snack, this assists in reducing PP glucose peak, but ensures adequate nutrition to the mother and the fetus. Excessive weight gain should be discouraged as it increases further the risk of delivering a large-for-gestational-age infant, adverse pregnancy outcome, and childhood obesity.The recommended weight gain during singleton pregnancy is dependent on pre-pregnancy BMI: 12.5-18 kg of weight gain for underweight women (BMI <18.5 kg/m2); 11.5-16 kg for normal weight (BMI 18.5-24.9 kg/m2); 7-11.5 kg for overweight (BMI 25-29.9 kg/m2), and 5-9 kg for obese (BMI ≥30.0 kg/m2).40

*Exercise*. Exercise has been shown to improve glycemic control in GDM. Daily moderate exercise for 30 minutes or more is recommended for a woman with GDM, if she has no medical or obstetrics contraindications. Advising GDM patients to walk briskly, or do arm exercises while seated in a chair for at least 10 minutes after each meal facilitates in reducing glucose rise post-meal, and help in achieving glycemic goal**.(9)**

***Pharmacological interventions. Insulin therapy***. If the medical nutrition therapy and exercise fail to achieve glycemic goals for a woman with GDM, insulin therapy should be initiated. The type and timing of insulin should be chosen based on the specific blood glucose elevation. If the fasting glucose is greater than 90-95 mg/dl (whole blood capillary) then basal insulin, long-acting insulin analog, or neutral protamine Hagedorn (NPH); 4 units for example, should be started before bedtime. If fasting glucose level is too high, then basal insulin dose can be calculated according to the patient's weight, 0.2 units/kg/day. In cases where glucose level is elevated following a meal, rapid-acting insulin, or regular

insulin should be prescribed before that specific meal, beginning with 2-4 units, or a dose of one unit per 10-15 g of carbohydrates. If both fasting and PP glucose levels are elevated, a 4-injections-per-day regimen “basal and meal time insulin regimen” should be prescribed.37 Basal and meal time insulin regimen is preferred over twice dose regimen because it is more likely achieves, maintains target blood glucose, and allows more flexibility. One could start by 2-4 units of rapid-acting insulin, or regular insulin before each meal, and 2-4 units of basal insulin before bed time. Another approach to determine the insulin doses is based on a woman’s body weight and gestational week. In the first trimester, the total daily insulin requirement is 0.7 units/kg/day, in the second trimester it is 0.8 units/kg/day, and in the third trimester it is 0.9-1.0 units/kg/day. In a morbidly obese woman, the initial doses of insulin may need to be increased to 1.5-2.0 units/kg to overcome the combined IR of pregnancy and obesity.37 Subsequently, the calculated total daily dose of insulin should be divided into 2 halves; one half given as basal insulin at bed time, and the other half divided between 3 meals, and given as rapid-acting, or regular insulin before meals. As insulin requirement may increase with the progression of pregnancy, it is crucial to follow patients’ SMBG regularly, and optimize their insulin doses.**(9)**

Pregnancy is associated with profound changes in metabolism, which facilitate the growth of a healthy fetus and prepare the mother and infant for the energy requirements in the postpartum period. After an initial anabolic stage, a physiologically beneficial increase in insulin resistance enhances fetal availability of metabolic substrates . In contrast, pre-pregnancy insulin resistance, as often observed in obese women, has been implicated in greater risk of gestational diabetes (GDM) and associated fetal adversity . While the metabolic response to pregnancy is recognised to be different in this increasingly prevalent subgroup of the antenatal population the pathways to GDM in obese women remain poorly described. This is of importance as less than one-third of obese women develop GDM. Insight into the metabolic adaptations to pregnancy and the pathophysiology of complications is facilitated by metabolomics technology**.(10)**

GDM has also been the focus of some recent metabolomic studies, although to date all have included participants from across the maternal weight spectrum, which is itself known to affect the maternal metabolome . None has addressed the metabolome in obese women prior to and at the time of GDM diagnosis. As no distinction is currently made in clinical practice between obese women of lower and higher GDM risk, we recently developed a prediction tool for GDM in obese women. Therefore, an algorithm including clinical factors and some conventionally measured biomarkers analysed early in the second trimester of pregnancy performed well, although the addition of more complicated metabolomic measures did not augment the performance of the tool **.(10)**

With increased prevalence over the last century, obesity in women of reproductive age has become amajor health problem in Turkey as it has throughout the world . Obesity and central adiposity are particularly frequent inwomen with PCOS and type 2 diabetes with an increased risk of pregnancy-related complications .

Maternal and neonatal complications such as gestational diabetes mellitus, pregnancy-induced hypertension, labor induction, failure of labor induction, cesarean delivery, macrosomia, shoulder dystocia and admission to neonatal intensive care units have been reported to increase with obesity . Furthermore, obesity is associated with an increased risk of uterine fibroids, which may affect pregnancy outcomes and require specific clinical management. There has also been reported to be an increase in obesity-related post-term pregnancy rates . Although the precise cause of the increase in the incidence of post-term pregnancies in obese pregnancies is not fully known, it has been suggested that it could be due to a decrease in the onset of spontaneous labor rates . The effect mechanism of obesity on the onset of spontaneous labor rate is not fully understood, but may be due to abnormal myometrial contractility caused by obesity, as this effect has been shown in in vitro studies . **(11)**

Both developed and developing countries are experiencing a rapid increase in the prevalence of obesity. In the UK, 24% of women of reproductive age are now obese (body mass index (BMI) equal or greater than 30 kg/m2) and the prevalence appears to be increasing. Studies in UK women show that the rates of

obesity in pregnancy have almost doubled in the last two decades. In the UK is at least 20% with 5% having severe or morbid obesity **.(12)**

Overweight and obesity are common problems with an increasing worldwide incidence. Australian data showed that 50% of pregnant women were overweight or obese and in the United States 36% of women were obese .

Maternal obesity and excessive gestational weight gain (GWG) have well recognized associations with preeclampsia, gestational diabetes mellitus (GDM), instrumental or operative delivery, failed induction, fetal macrosomia, neonatal hypoglycaemia, perinatal mortality and infant and childhood obesity . In addition, maternal obesity is the single most common modifiable factor in stillbirth in the developed world . There is limited published data assessing the relationship between a woman's actual and perceived Body Mass Index (BMI) in pregnancy, and the effect this has on GWG. It has been demonstrated that overweight and obese pregnant women are less likely than women of normal weight to correctly assess their own BMI, and that overweight women who underestimate their BMI are more likely to gain excess weight in pregnancy. In addition to assessing pregnant women's accuracy in estimating their own BMI. (**13)**

**G**estational diabetes mellitus (GDM), or glucose intolerance that begins or is first recognized during pregnancy, affects 7% of pregnancies, representing 200,000 cases annually in the U.S. The risk of GDM is higher among women who are obese, and the recent dramatic increase in obesity prevalence in the U.S. mirrors a worrisome rise in the prevalence of GDM . Future individual health and societal medical costs could be substantial as obesity and GDM not only increase the risk of adverse pregnancy and infant outcomes but also are associated with a higher risk of developing type 2 diabetes later in life in both the mother and child.

Despite the number and consistency of studies reporting a higher risk of GDM with increasing body weight or BMI, the magnitude of this association remains un certain. This is due in part to the wide variation in reported GDM prevalence among different populations, as well as the lack of consistency in diagnostic methods and definitions for GDM **. (14)**

Gestational diabetes mellitus (GDM) can be defined as different levels of abnormal glucose intolerance that occur for the first time during pregnancy . It has affected 0.5–15% of pregnancies in the world and is one of the most common diseases of pregnancy . Additionally, GDM is an important factor causing adverse pregnancy outcomes, which is hazardous for the mother and the newborn . There are increased risks of eclampsia, preeclampsia, gestational hypertension, and future type 2 diabetes for the mother. Several recent studies found several predisposing factors for GDM, such as age, obesity, and familial history of diabetes . However, pre pregnancy and maternal obesity are important factors, which also increases related pregnancy complications such as preeclampsia and fetal growth disorders. There is a growing prevalence of maternal obesity worldwide. Nowadays, body mass index (BMI) is used to evaluate the risk stratification of obesity-related pregnancy complications in clinics . However, BMI cannot reflect fat distribution or the proportion of adipose to non adipose tissue . Adipose tissue not only is a storage area for energy but also acts as an endocrine and immune organ that releases signals . Therefore, excessive accumulation of adipose tissue affects body physiology, giving rise to chronic inflammatory responses and disarranging metabolic homeostasis. Hence, maternal central obesity is significant and can reflect fat distribution or the proportion of adipose to non adipose tissue **.(15)**

As recommended, obesity and type 2 diabetes mellitus (T2DM) have become escalating global health problems. In 2016 worldwide obesity, defined by a body mass index _30 kg/m2, had a prevalence of 13.1% among the age group 181 years compared with 5.3% in 1980. Importantly obesity is a major risk factor for T2DM, hence the number of people with diabetes mellitus, about 90% of whom are T2DM, has risen from 108 million in 1980 to 422 million in 2014. This represents an 8.5% global prevalence of diabetes mellitus among adults over 18 years in 2014. Projections of the International Diabetes Federation expect this number to increase to about 500 million in 2045. Derangements of the maternal glucose-insulin axis as in pre gestational (type 1 diabetes mellitus [T1DM] and T2DM) and gestational diabetes mellitus (GDM) and maternal obesity increase

the risk of both mother and offspring to develop obesity and T2DM later in life. Thus, an obese pregnant woman or a woman with T1DM, T2DM, or GDM confers a risk for the offspring to become obese and also to later develop T2DM. Female offspring born to such a pregnancy may themselves become pregnant when already overweight or obese, which in turn increases the risks for the**..** next generation. This sequence constitutes a self-perpetuating cycle that contributes to the obesity and T2DM epidemic that we are seeing.

For this reason obesity in the youth is especially alarming. In Europe more than 20% of children are overweight or obese by the age of 10 years. Epidemiologic evidence demonstrates that being born with excessive adiposity (often described as "macrosomic" or large for gestational age at birth) strongly associates with overweight or obesity in youth, commonly with features of the metabolic syndrome. These associations are independent of ethnicity and genetics and are likely mediated through epigenetic changes, which may be induced by fetal hyperglycemia, hyperinsulinemia, or other metabolic disturbances in fetal development. For example, offspring born to obese women not only store more triglycerides, but also have a greater number of adipocytes by the age of 2 years.**(16)**

The epidemic of childhood obesity that has occurred in the past 20 years is associated with an increase in the prevalence of type 2 diabetes mellitus (T2DM) among children and adolescents. By 1994, _14% of children and 12% of adolescents were overweight, as defined by a BMI of _85th percentile for age,and recent data indicate that the prevalence of obesity has continued to increase. The increased obesity was accompanied by an increase in T2DM among adolescents, from _5% of new cases of diabetes in 1982 to _45% (depending on geographic location) in 1999. There are a number of risk factors for T2DM among children and adults in addition to obesity. A well-recognized risk factor among adults is the metabolic syndrome (MS), also called syndrome X, which was first described in the 1950s and predisposes individuals to diabetes and cardiovascular disease. MS is defined as the association of obesity, insulin resistance, glucose intolerance, hypertension, and a characteristic dyslipidemia. There is a growing body of literature on the prevalence of components of the MS among obese

children and adolescents. This raises great concern about the potential development of not only T2DM but also early stages of cardiovascular disease in childhood.**(17)**

Pre pregnancy obesity (body mass index [BMI] ≥ 30 kg/m2) (World Health Organization), is awell-documented risk factor for obstetric complications, including gestational diabetes mellitus, hypertension, cesarean delivery, miscarriage, stillbirth, fetal macrosomia, preterm birth, and select birth defects. However data about obesity trends among pregnant women in the US are limited. **.(18)**

Gestational diabetes mellitus (GDM), like type 2 diabetes (type 2 DM), is characterized by metabolic defects of insulin resistance and relative insufficiency of insulin secretion. As with type 2 DM, ethnicity-associated factors may play a role in the development of GDM . Indeed, women belonging to certain ethnic groups, such as Asians and South Asians, exhibit an increased risk of developing GDM . Despite this risk differential, however, there has been limited study of ethnic differences in insulin dynamics during pregnancy. In a cross-sectional study in late pregnancy, reported that Asian women develop GDM at lower body mass index (BMI) than Caucasians but found no differences in insulin resistance and pancreatic -cell function between the two ethnic groups. ...(**19**)

High pre-pregnancy body mass index (BMI) and excessive gestational weight gain (GWG) are associated with many un favourable maternal and neonatal outcomes. Overweight/obese women should be counselled regarding their body weight before conception, however, most women have access to obstetricians only when they are pregnant. Among the interventions aimed at preventing excessive GWG, few have demonstrated efficacy in high-risk, the principal issues are population heterogeneity , the interventional methods, and the timing of the interventional programmes. Additionally, lifestyle interventions did not have a substantial effect on other clinical outcomes. Dietary advice to prevent gestational diabetes mellitus (GDM) appears to be beneficial in general, although the results are overly heterogeneous. **(20)**

The prevalence of obesity is increasing both in developed countries and in developing countries, and obesity is considered to be a global pandemic. An estimated one fifth of pregnant women in the United Kingdom and one third of those in the United States are obese. Obesity during pregnancy is associated with an increased risk of adverse short-term and long-term consequences for both mother and baby. Attempts at reducing the incidence of pregnancy complications associated with obesity have focused on dietary and lifestyle interventions, but these have generally been unsuccessful. An alternative strategy is the use of metformin, which reduces insulin resistance. Metformin has been used extensively in the treatment of gestational diabetes mellitus, and there has been no evidence of an increase in the incidence of birth defects associated with its use. Hyperglycemia and increased insulin resistance occur with obesity and may explain the association between obesity and fetal macrosomia, as well as other pregnancy complications. Studies involving women with gestational diabetes mellitus have shown that metformin reduces gestational weight gain**.(21)**

researches referred that,in 2009–2010, 36% of adult women and 16% of children and adolescents in the United States were reported to have a body mass index (BMI) in the obese range (≥30 kg/m2). This number is projected to increase to 42% in adults by the year 2030. With rates of both adult and adolescent obesity increasing, the prevalence of obesity among women of child bearing age (aged 15–44 y) can also be expected to increase. Population and cohort studies consistently indicate that obesity is associated with an increased risk of comorbid conditions during pregnancy, cesarean delivery, anesthesia complications, venous thromboembolism and maternal mortality. Obesity also has implications for the fetus, which may suffer short term consequences resulting from medically indicated preterm birth and macro somia, and also long-term implications related to fetal in utero programming. **(22)**

Available studies suggest that, gestational diabetes mellitus (GDM), defined as carbohydrate intolerance leading to hyperglycemia first recognized during pregnancy, is associated with increased risk for pregnancy and delivery

complications, including cesarean section, infant macrosomia, and neonatal hypoglycemia **.(23)**

It is recommended, In pregnant women with pre-existing diabetes mellitus (DM), physiological changes in insulin sensitivity lead to substantially higher rates of perinatal complications than seen amongst the general population ,High levels of glycemia during pregnancy may be associated, among other complications, to excessive fetal weight and length, neonatal hypoglycemia and other**..** metabolic disorders, and an increased risk of obesity and type 2 DM in adulthood for the newborns Pregnant women with DM have an increased risk of hypertensive pregnancy syndromes,premature delivery, cesarean delivery, and obstetric trauma, Moreover, as gestation is a time when women naturally gain weight, it may itself predispose to obesity, due to an increase in postpartum weight retention, if this gain is excessive. Healthy eating is one of the key factors to meet increased maternal nutritional demand and promote adequate fetal growth and development, and represents one of the pillars of adequate glycemic control, Since the Diabetes Control and Complications Trial, carbohydrate counting has been described as an important dietary planning method for people with diabetes, associated with reduced glycated hemoglobin (HbA1c) and increased quality of life. This method is characterized by greater autonomy and flexibility of food choices, with regular nutritional education guidelines and actions being essential to ensure the quality of the diet. In 2014, the food guide for the Brazilian population drew attention to the relationship between food choices and health. In the guide, the consumption of fresh or minimally processed foods is encouraged, and the consumption of ultra-processed foods is proscribed. Recent evidence points to the negative effects of the consumption of ultra-processed foods on the lipid profile, weight gain, and prevalence of metabolic syndrome in different populations.**.(24)**

## CHAPTER 3

## CONCLUSIONS AND RECOMMENDATIONS

The negative impact of obesity before and during pregnancy on mothers' and their babies' health is clear. Health conditions such as gestational diabetes, pre-eclampsia and gestational hypertension are common in pregnant women with obesity. There is also an increased rate of instrumental and caesarean section births, and a greater rate of surgical site infections and antenatal and postnatal depression. The risk of large for gestational age babies is higher, and lower breastfeeding initiation rates and shorter breastfeeding duration are also seen. In addition, obesity is linked to a greater risk of pre-term birth, fetal defects, congenital anomalies, and perinatal death. These adverse outcomes lead to increased costs, due to longer duration of hospital stay and higher treatment costs. Investing in national subsidized programmes aimed at supporting women to lose weight before they conceive, and control their weight in pregnancy, may thus confer long-term health and monetary benefits. Research that is needed in this area, in addition to updates systematic reviews, includes: qualitative studies on women's perspectives of breastfeeding, in order to understand their infant feeding decisions and behaviour, and explorations of why pregnant women with obesity suffer from poorer mental health compared to those of healthy weight.

Research into effective pre-conception interventions to help women with obesity lose weight before they conceive, and between pregnancies, is also essential, in order to reduce the burden of maternal and fetal outcomes caused by maternal obesity. In addition, observed that cycling exercises initiated early in pregnancy and performed at least 30 minutes 3 times per week had a significant effect on lowering the risk of GDM in overweight and obese pregnant women and may affect their offspring size at birth. And the decrease of GDM is very relevant to the reduced gestational weight gain in pregnancy. Furthermore, such exercise does not increase the risk of preterm birth or reduce the mean gestational age

at birth and should therefore be recommended. Thus, in the absence of contraindications, regular exercise should be recommended as an important part of antenatal care, and there is the need for a well-designed large-scale prospective trial which examines combined antenatal lifestyle interventions in obese pregnant women that is suitably powered and incorporates robust methodology in accordance with standards set by Medical Research Council's framework for evaluating complex interventions. In order to reduce the number of overweight and obese pregnant women increasing in high income and middle income countries. Environmental changes could lead to increased caloric supply and decreased energy expenditure among women. National and local governments should work together to create a healthy food environment.

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