Gestational Diabetes Mellitus; Mother and Infant Outcome (Review)

Faiza Nouh 1*, Mariam Omar 2, Manal Younis 3,
1-2Department of Nutrition, Faculty of Public Health, Benghazi University, Benghazi, Libya
3Royal College of Obstetrics and Gynecology, Cumh Cork University Maternity Hospital, Cork Ireland

Abstract: Gestational Diabetes Mellitus is commonly recognized as a state of physiological and temporary insulin resistance. A gestational diabetes complicated pregnancy is still associated with a high perinatal risk with increased neonatal mortality and morbidity. Currently, the incidence of gestational diabetes is increasing with many complications for both mother and the child. This concept opens a new horizon for a study being conducted to get a more clear idea about this drastic effect and awareness. The review studies have recommended the importance of the screening and early management of gestational diabetes mellitus in preventing the adverse effects on mothers and fetuses. Also, studies are recommending increasing awareness about the risks of complications associated with gestational diabetes by education for pregnant women and families. This review will try to draw a picture about gestational diabetes mellitus and its complications.

Keywords: Gestational, Diabetic, Pregnant, complication infant and mother

INTRODUCTION

According to World Health Organization (WHO), International Association of Diabetes in Pregnancy Study Groups (IADPSG) and American Diabetic Association (ADA) the definition of gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy. However, the precise level of glucose intolerance characterizing gestational diabetes has been controversial over the last three decades[1,6]. Diabetes during pregnancy is classified as pre-gestational diabetes which can be type 1 diabetes, type 2 diabetes, or secondary diabetes. Gestational diabetes; impaired glucose tolerance of pregnancy, impaired glucose tolerance (IGT) is intermediate conditions in the transition between normality and diabetes.

People with IGT or impaired fasting glucose (IFG) are at high risk of progressing to type 2 diabetes, although this is not inevitable [5]. Undiagnosed pre-existing diabetes, undiagnosed pre-existing impaired glucose tolerance can also developed to GDM[7]. The prevalence of GDM varies worldwide and depends on the population being studied and the diagnostic tests employed. Approximately 40% of women with GDM who are obese before pregnancy develop type 2 diabetes within 4 years [7]. A retrospective United Kingdom (UK) study of 287,213 pregnancies between 1989 and 1997 showed that after adjusting for ethnic group, parity, maternal age and history of hypertension, women with a Body Mass Index (BMI) ≥ 30 kg/m² were more likely to develop GDM than women with a BMI of 20.0-24 kg/m² [8,9]. These findings were similar to a later Australian study of 14,230 pregnancies after corrected for maternal age, parity, ethnicity, educational and smoking status, which showed that the developing of GDM was 2.95 times higher in obese women (BMI 30.01-40.00 kg/m²) compared with normal-weight (BMI 20.01-25.00 kg/m²) women[10].

In United States, GDM occurs in 5 to 9 percent of all pregnancies and is growing in prevalence [9], while the prevalence of GDM according to ethnicity among American Caucasian is about 1.5% - 4%. The prevalence of GDM among native American is up to 20% depending on the difference between tribes, but African American have found the relative risk was listed as 3-4 times that of whites, which would put the implied percentage at about 4.5% -16%. (11) In 2011, study showed prevalence of GDM in Qatar to be 6.4%, Compared to the regional studies in the Middle East: in Iran (2.6%-4.8%), Bahrain (5.4%).

At the international level, 4.7% among Chinese, 5.5% in Sri Lanka, and 5.7% in Thailand. The prevalence of GDM in Saudi Arabia is about 7% to 14%. Other study from Iran collectively 18 surveys were assessed from 1992 to 2007, GDM ranged between 1.3% and 10%. The prevalence of GDM in South Africa was 1.5%, while the prevalence of GDM
in North Africa is 27.8%, while in Egypt and Arab countries is (7.2%), while is 5.4% in Algeria [12]. In European the prevalence is about 1-3%. In Australia, at least 17,000 women develop GDM every year. Between 5% to 8% of pregnant women will develop gestational diabetes and this usually occurs around the 24th to 28th week of pregnancy [10, 13]. GDM can affect the women during pregnancy and may be cause complications for mothers and infants, some of these complications are serious. For this reason, the screening and early diagnoses for diabetic women are very significant and mainly if the mothers have risk factor(s) for diabetes, the mother needs management to minimize the risk of complication [13, 14]. Accordingly, life-style modification throughout diet and exercise are important approach to bring down the glucose level and improve the overall health status. The aim of this study is reviewing the management of GDM through screening and early diagnosis to minimize the complications for mothers and babies [6,7,10,15].

MATERIALS AND METHODS
Searching on the internet using the Google search engine using the keywords: management of gestational diabetic mother and complication in infant and mother. The search resulted (201) sources of which the most relevant; and actually used were (29) articles. These (29) were considered of most relevance because they answered the aim and objective of the review; they presented accurate information based on appropriate methodology. These data search was undertaken to identify previous studies that focused on management gestational diabetic mother and its relation to complication for mother and infant. All studies reviews were written in English. The study period was from March to the end of October 2016.

DISCUSSION
Risk factors
Many maternal factors and characters increase the risk of developing GDM. Age greater than 25 years were more likely to develop GDM. Parity (≥ 3) is strongly associated with GDM. The parity seems to be independent of the increasing weight and age that usually accompany increasing parity[2,9]. Excess weight is another strong contributing factor. Pregnant woman who had pre-pregnancy (BMI) 27kg/m² and above are more likely to develop GDM[16-18]. Short stature , low birth weight, α-Thalassemia trait are other common risk factors of GDM. Polycystic ovary syndrome (PCOS) is characterized by chronic anovulation and hyperandrogenism; it has been linked to obesity, type 2 diabetes mellitus, dyslipidaemia, hypertension, and heart disease[19]. PCOS is a common risk factor of GDM. IGT or IFG (blood sugar levels are high, but not high enough to be diabetes)[19]. A previous child over 4000g (almost 9 lbs) indicates a fairly high risk of GDM in subsequent pregnancies, although macrosomia can also be due to genetic size inheritance as well as maternal hyperglycemia/fetal hyperinsulinemia. Previously giving birth to a stillborn infant has identified as a strong associated factor with GDM[20-23]. Furthermore, a previous pregnancy with GDM is very strongly associated with recurrence. Chances are generally cited as 2 of 3, with it often recurring earlier and more severely, although some studies show the rate of recurrence as lower[10]. It should be noted that it does not always recurrent had a mild case of GDM in her first pregnancy but avoided its recurrence in subsequent pregnancies by being very proactive. Polyhydramnios is sometimes associated with GDM. Physically inactive is a big risk factor for diabetes. Moreover, women who eat a diet high in fiber prior to becoming pregnant are less likely to get GDM [12,14]. It has found that every 10 grams of fiber in daily diet can decrease risk of GDM by 26 percent. Family history is another very strongly associated with GDM, especially when a first-degree relative had diabetes [17,24-27]. Regarding pregnancy risk factors; high blood pressure in pregnancy is being associated with GDM. Multiple pregnancies often have an increased risk for developing occurrence of problems like GDM and pre-eclampsia [26]. Mothers with twins or more should be monitored earlier and possibly more frequently. Increased iron stores; when body iron is excessive, oxidation can harm the sensitive beta cells of the pancreas [20,28,29].

Pathogenesis
Pregnancy is a diabetogenic condition characterized by insulin resistance with a compensatory increase in β-cell response and hyperinsulinemia. Insulin resistance usually begins in the second trimester and progresses throughout the remainder of the pregnancy. Insulin sensitivity is reduced by as much as 80%. Placental secretion of hormones, such as progesterone, cortisol, placental lactogen, prolactin, and growth hormone, is a major contributor to the insulin-resistant state seen in pregnancy. The insulin resistance likely plays a role in ensuring that the fetus has an adequate supply of glucose by changing the maternal energy metabolism from carbohydrates to lipids [5,11,22,27]. Women with GDM have a greater severity of insulin resistance compared to the insulin resistance seen in normal pregnancies. They also have an impairment of the compensatory increase in insulin secretion. Women with GDM had a 67% reduction in their β-cell compensation compared with normal pregnant control subjects. There is also a subset of women with GDM who have evidence of islet cell autoimmunity. The reported prevalence of islet cell antibodies in women with GDM ranges from 1.6 to 38%. The prevalence of other islet auto antibodies, including insulin auto antibodies and glutamic acid decarboxylase antibodies, has also been variable. These women may be at risk for developing an autoimmune
form of diabetes later in life. Finally, in ~5% of all cases of GDM, the β-cell's inability to compensate for the insulin resistance is the result of a defect in the β-cell, such as a mutation in glucokinase [2,17,27].

Screening
Screening is performed to select individuals to be investigated. Since 1999, the WHO has recommended the screening of all women or all women except those considered low-risk [22]. According to the ADA guidelines, patients should be screened for risk factors for GDM at their initial visit. A woman is considered high risk if she has one or more of the following: marked obesity, personal history of GDM, glucose intolerance or glycosuria, or a strong family history of type 2 diabetes. A woman is considered low risk if she meets all of the following criteria: age < 25 years, normal pre-pregnancy weight, not a member of an ethnic/racial group with a high prevalence of diabetes (e.g., Hispanic American, Native American, Asian American, African American, or Pacific Islander), no known diabetes in first-degree relatives, no history of abnormal glucose tolerance, and no history of a poor obstetric outcome. A woman is considered intermediate risk if she does not fall into either the high- or low-risk category[6]. If a woman is high risk, glucose testing should be done as soon as possible. If the initial testing is negative, the woman should be retested between 24 to 28 weeks of gestation. If she is intermediate risk, she should undergo glucose testing at 24 to 28 weeks [6,22,25]. The ADA recommends two approaches to screening for GDM if a woman has one or more risk factors—a one-step or a two-step approach. The more commonly used two-step approach involves initial non fasting screening with the 50-g oral glucose challenge test, followed by a 1-hour serum glucose concentration. If the glucose level exceeds the glucose threshold value on this test, the patient is further evaluated with the diagnostic OGTT, as follow: A 1-hour glucose value >140 mg/dl identifies ~80% of women with GDM. A 1-hour glucose value >130 mg/dl identifies ~90% of women with GDM, but it has a higher false positive rate. Either value is accepted by the ADA and the American College of Obstetricians and Gynecologists (ACOG) as abnormal. The one-step approach requires a diagnostic OGTT without prior screening with the 50-g 1-hour glucose challenge test. This may be cost-effective in some high-risk patients. Of note, if a patient has a fasting plasma glucose level > 126 mg/dl or a random plasma glucose level > 200 mg/dl, this meets the threshold for diabetes mellitus and should be confirmed on a subsequent day [6].

Diagnosis
The oral glucose tolerance test (OGTT) is the most commonly used test to diagnose GDM [2]. This test involves quickly drinking a sweetened liquid, which contains 50g of sugar. The body absorbs this sugar rapidly, causing blood sugar levels to rise within 30-60 minutes. A blood sample will be taken from a vein in your arm 1 hour after drinking the solution. The blood test measures how the sugar solution was metabolized (processed by the body) 13. According to diagnostic criteria recommended by the ADA, GDM is diagnosed if two or more plasma glucose levels meet or exceed the following thresholds: fasting glucose concentration of 95 mg/dl, 1-hour glucose concentration of 180 mg/dl, 2-hour glucose concentration of 155 mg/dl, or 3-hour glucose concentration of 140 mg/dl. These values are lower than the thresholds recommended by the National Diabetes Data Group and are based on the Carpenter and Coustan modification. The ADA recommendations also include the use of a 2-hour 75-g OGTT with the same glucose thresholds listed for fasting, 1-hour, and 2-hour values. The WHO diagnostic criteria, which are used in many countries outside of North America, are based on a 2-hour 75-g OGTT. GDM is diagnosed by WHO criteria if either the fasting glucose is > 126 mg/dl or the 2-hour glucose is > 140 mg/dl [6,13].

Complications
Various physiological and hormonal changes of pregnancy have a significant effect on diabetes in pregnancy, and can exacerbate complication of diabetes such as nephropathy and retinopathy. Deteriorations in these conditions tend to revert to normal after delivery. Complications of pregnancy consequent upon pre-existing diabetes are commonly separated into maternal and fetal [1]. The outcome of pregnancy among mothers with GDM is still worse than that of non-diabetic women [24]. Fetal complication includes macrosomia which defined as birth weight more than 4,000g. When the maternal blood has too much glucose, the pancreas of the fetus senses the high glucose levels and produces more insulin in an attempt to use this glucose. The fetus converts the extra glucose to fat. Even when the mother has GDM, the fetus is able to produce all the insulin it needs. The combination of high blood glucose levels from the mother and high insulin levels in the fetus results in large deposits of fat, which causes the fetus to grow excessively large [19]. Macrosomia occurs in about 20-30% of infants whose mothers have GDM [6]. Fetal hypoglycemia: it refers to low blood sugar in the fetus immediately after delivery. This problem occurs if the mother's blood sugar levels have been consistently high, causing the fetus to have a high level of insulin in its circulation. After delivery, the baby continues to have a high insulin level, but it no longer has the high level of sugar from its mother, resulting in the newborn's blood sugar level becoming very low. Jaundice is another and more common in newborns of mothers who had diabetes during their pregnancy. Jaundice usually goes away, but the baby may need to be placed under special lights to help. Neonatal polycythemia which means more red

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blood cells than normal this may cause a blockage in the blood vessels or hyperbilirubinemia is another form of fetus complication. Other complications can affect the fetus such respiratory distress syndrome and having breathing problems perinatal mortality, congenital malformation, hypocalcaemia, Immature lungs, Small left colon syndrome - causes symptoms of intestinal blockage, Stillbirth [6,10,14,19].

On the other hand, there are several maternal complications due to GDM. Polyhydramnios is a common form of GDM maternal complications. It is thought to be related to the size of the placenta and diabetic control. It is a high risk pregnancy condition where an excess amount of amniotic fluid surrounds the unborn infant. The amniotic fluid plays an important role in the fetus' motor development in the womb. The incidence of polyhydramnios in diabetes is 5-13 per cent where the control is good, but may be as high as 22-26 per cent where it is poor [10]. Another complication is Preeclampsia (PE); it makes about 10-30% of women with GDM develop preeclampsia. The incidence of PE among GDM mothers increases with both the severity of GDM and the pre-pregnancy BMI. Preeclampsia can harm the pregnant women by causing seizures or a stroke. PE predisposes the patient to perinatal complications such as perinatal death, prematurity and intrauterine growth retardation. Furthermore, the rate of caesarean section in diabetic pregnancies is significantly higher than that in non-diabetic pregnancies, and may be as high as 50 per cent. This is partly due to fetal macrosomia with a consequent fear of shoulder dystocia complication macrosomic vaginal deliveries, and also due to failed induction of labour [12,18].

Long term effects

The immediate effects of intra-uterine death, birth trauma and neonatal hypoglycemia have been well documented. The offspring of women with GDM are more likely to develop obesity, diabetes, and cardiovascular disease. There are also data which show a link between high birth weight and breast cancer. Some of this may be the result of a genetic predisposition but it is interesting to note that gestational diabetes is transmitted preferentially (though not exclusively) through the maternal line. There is speculation that the uterine milieu leads to metabolic imprinting which influence the risk of certain diseases in adulthood. This raises the possibility that therapeutic modulation of maternal glycaemic state might prevent the fetus form developing certain diseases in later life [3].

It has been shown women with history of GDM have about 30% risk of developing type 2 DM in later life. This compares with a rate of 8% in the general population. Given the rising incidence of type 2 DM and earlier age at onset, it seems likely that this risk is set to increase. This constitutes a significant health risk with higher rate of cardiovascular disease and premature death [3]. Women who have had gestational diabetes have a 60% increased risk of developing type 2 diabetes later-in-life. In addition, women who have gestational diabetes during one pregnancy have a 40%-50% chance of developing diabetes in the next pregnancy [13].

MANAGEMENT AND TREATMENT

The main goal of GDM management is to reduce the risk for both mother and her infant after pregnant women diagnosed with gestational diabetes, mother will need to make changes in what she eats, and she will need to learn to check the blood sugar level. In some cases, mother will also need to learn how to give herself insulin injections [13,15]. Treatment of gestational diabetes is aiming to reduce the risk of complication for mother and infant such as, shoulder dystocia (its occurs because baby have macrosomia), polyhydramions, PE, type 2 DM, respiratory distress syndrome , neonatal polycythemia ,hypoglycemia , jaundice [15]. Moreover, changes in diet will help the pregnant to make a healthy eating plan with food choices that are good for both the mother and her baby. These choices are recommended to follow by mother throughout pregnancy and after[10]. The dietitian will learn pregnant women to make changes in her diet. The changes include avoidance high-calorie snacks and desserts, including soda with sugar, fruit punch, candy, chips, cookies, cakes, and full-fat ice cream. Pregnant can use artificial sweeteners, such as aspartame, sucralose, stevioside, or acesulfame potassium. These sweeteners have not been linked to an increased risk of birth defects. Eat a lot of vegetables and fruits, at least five servings a day is highly recommended for pregnant women. Some fruits (like grapes, dried fruit) can increase the blood sugar level excessively and should be eaten in limited amounts. Moreover, pregnant mother should not eat a lot of starch vegetables such as potatoes. However, eating as many non-starchy fruits or vegetables as mother likes is highly recommended. Choose foods with whole grains. This includes whole-wheat bread, brown rice, or whole-wheat pasta instead of white bread, white rice, or regular pasta is significant for both mother and fetus health. Eat a small amount of red meat and only a few times during the week. Pregnant mother should choose lean cuts of meat that end in "loin" (e.g. tenderloin, sirloin), and mother should remove skin from chicken and turkey before eating. Choose low- or fat-free dairy products, such as skim milk, nonfat yogurt, and low-fat cheese. Use liquid oils (olive, canola) instead of solid fats (butter, margarine, shortening) for cooking [10]. If pregnant mothers were overweight before she got pregnant the midwife or specialist will recommend her cut down on calories and do at least 30 minutes' exercise a day.
early pregnancy study found that third-trimester postprandial glucose levels were the strongest predictor of percentile birth weight in women with GDM who require insulin therapy, adjustments of their insulin regimens based on postprandial, rather than pre-prandial, glucose levels decreased the incidence of neonatal hypoglycemia, macrosomia, and cesarean delivery for cephalopelvic disproportion [6,8,10,14,15,17].

Insulin

Insulin therapy is the most commonly used treatment when medical nutrition therapy fails to maintain blood glucose levels at the desired ranges or when there is evidence of excessive fetal growth. A large, prospective, population-based study of almost 2,500 women with GDM compared the effect of intensive versus conventional management of GDM. The women randomized to the intensive management group were given memory reflectance meters and instructed to monitor their blood glucose seven times per day (fasting, pre-prandial, 2-hour postprandial, and bedtime). The women in the conventional management group were instructed to monitor four times per day (fasting and 2-hour postprandial) in addition to weekly fasting and 2-hour postprandial glucose measurements during clinic visits. Both groups were treated with diet and insulin as needed to reach the following goals: overall mean blood glucose 90-100 mg/dl, fasting blood glucose 60-90 mg/dl, and postprandial blood glucose < 120 mg/dl. Overall, 66% of the women in the intensive management group were treated with insulin versus 36% of women in the conventional management group. This study demonstrated a decreased rate of macrosomia, cesarean section, fetal metabolic complications, shoulder dystocia, neonatal intensive care unit days, and respiratory complications in the intensive management group. Another important consideration of this study is that GDM was defined as only one or more abnormal OGTT values, rather than the current standard of two or more abnormal glucose levels. Other studies have also shown improvement in rates of macrosomia and other maternal and fetal complications by treating women who do not meet the criteria for GDM but who have evidence of impaired carbohydrate tolerance as determined by an abnormal screening 50-g glucose challenge test and/or one or more abnormal results on OGTT [6,10,15,13].

Oral Agents

Oral hypoglycemic agents (glyburide and metformin) have been shown to be a possible alternative to insulin in the medical treatment of GDM. Women treated with oral hypoglycemic agents were compared with those treated with all types of insulin. Two trials compared insulin to glyburide; one trial compared insulin, glyburide, and acarbose; and one trial compared insulin to metformin. No significant

Glucose Monitoring

Self-monitoring of blood glucose is recommended for women with GDM. The goal of monitoring is to detect glucose concentrations elevated enough to increase perinatal mortality. The Fourth International Workshop-Conference on GDM recommends maintaining the following capillary blood glucose values: pre-prandial glucose < 95 mg/dl, 1-hour postprandial glucose < 140 mg/dl, and 2-hour postprandial glucose < 120 mg/dl. (3) ACOG guidelines are the same except that the 1-hour postprandial glucose value is considered acceptable at either 130 or 140 mg/dl. A study suggests guidelines that are a little stricter: fasting glucose < 90 mg/dl and 1-hour postprandial glucose < 120 mg/dl. (28) One prospective study of 668 patients (334 with GDM and 334 control subjects) found that women with GDM who had a mean blood glucose level between 87 and 104 mg/dl had incidence rates of intrauterine growth retardation (IUGR) and large for gestational age (LGA) infants comparable to the control group. However, women who had mean blood glucose values < 87 mg/dl had a higher incidence of infants with IUGR, whereas women who had mean blood glucose values > 104 mg/dl had a higher incidence of LGA infants. This study suggests that although it is important to treat hyperglycemia in GDM, it is also important not to over treat because this can increase the risk of IUGR. It is important for women to check postprandial glucose levels because these have been shown to correlate more with macrosomia than do fasting levels. The diabetes in
CONCLUSION
Gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy. Pregnancy is a diabetogenic condition characterized by insulin resistance with a compensatory increase in β-cell response and hyperinsulinemia. Insulin resistance usually begins in the second trimester and progresses throughout the remainder of the pregnancy. Insulin sensitivity is reduced by as much as 80%. The prevalence of GDM varies worldwide and depends on the population being studied and the diagnostic tests employed. Approximately 40% of women with GDM who are obese before pregnancy develop type 2 diabetes within 4 years. The GDM can occur when mothers have a risk factors such as age greater than 25 years, parity (≥3), excess weight if MBI ≥ 27, short stature, low birth weight, polycystic ovary syndrome, impaired glucose tolerance, a previous child over 4000g, physically inactive, type of the diet, family history, high blood pressure in pregnancy, increased iron stores. Various physiological and hormonal changes of pregnancy have a significant effect on diabetes in pregnancy. Complications of pregnancy consequent upon pre-existing diabetes are commonly separated into maternal and fetal complications. Fetal complication include significantly increased risk of macrosomia, hypoglycemia, jaundice, respiratory distress syndrome, neonatal polycythemia, perinatal mortality, congenital malformation, hypocalcaemia, immature lungs, small left colon syndrome - causes symptoms of intestinal blockage. Stillbirth. Maternal complications include polyhydramnios, cesarean delivery, preclampsia. The main goal of GDM management is to reduce the risk for both mother and her infant after pregnant women diagnosed with gestational diabetes, mother will need to make changes in diets, and pregnant women will need to learn how to check the blood sugar level. In some cases, mother will also need to learn how to give herself insulin injections. Moreover, adapting a daily exercise program as an adjunct to treatment, helps mothers body to use insulin effectively.

REFERENCES


