Gestational Diabetes Mellitus (GDM): Current concept and a short Review

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Abstract

Gestational Diabetes Mellitus (GDM) is a very common and important disease occurring during pregnancy and has detrimental effect on both the mother and the baby. The mother is at increased risk of developing obstetric complications like prolonged labour, prone to develop type 2 diabetes in future and the baby is born with overweight, cause of childhood obesity and later life development of type 2 diabetes. A short review and current concept of GDM is discussed.

Key words: *GDM, Type 2 diabetes, Obesity, Macrosomia,Complications*

Introduction

Gestational Diabetes Mellitus is defined as Carboh ydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy[1]. Women who become pregnant and who are known to have diabetes mellitus before pregnancy do not have gestational diabetes but have "diabetes mellitus and pregnancy" should be treated accordingly before, during and after pregnancy.

Review of literatures and discussion:

Gestational diabetes affects 3-10% of pregnancies depending on population studied[2,3]. No specific cause has been identified , but it is that hormones produced during pregnancy increase in women 's resistance to insulin resulting in impaired glucose tolerance.

When born to mother with gestational diabetes babies are at increased risk of problem such as being large for gestational age which may lead to delivery complications, low blood sugar and Jaundice. Women with GDM are at increased risk of developing type 2 diabetes mellitus after pregnancy, while their off spring are prone to develop childhood obesity with type 2 diabetes in later life[4,5].

One study has shown that Maternal gestational diabetes mellitus increases the offspring's cardio metabolic risk, and in utero hyperinsulinemia is an independent predictor of abnormal glucose tolerance in childhood[6]. In GDM cord blood leptin levels are significantly higher, and a source other then fetal adipocytes appears to contribute to this[7]. Women diagnosed with GDM who had gestational weight gain above the IOM guidelines have higher risk of undesirable outcomes, including preterm delivery, having macrosomic neonates, and cesarean delivery. Women who gained below guidelines are more likely to remain on diet control but have small for gestational age neonates[8]. Maternal adipocyte fatty acid binding protein (AFABP) concentrations are significantly increased in GDM. The adipokine might contribute to the increased metabolic and cardiovascular risk of the disease[9]. Raised GGT Level in an independent risk factor for GDM in high risk pregnant women[10].

Serum levels of adipocyte fatty acid binding protein are increased in gestational diabetes mellitus[11]. Another study suggest that moderate maternal leisure time physical exercise during GDM pregnancy may reduce the risk of delivery[12]. Visfatin concentration is decreased in women with gestational diabetes mellitus in the third trimester[13].

Gestational diabetes mellitus (GDM) affects approximately 4% of all pregnant women in the US and represents 90% of all cases of diabetes mellitus diagnosed during pregnancy. In addition of the adverse pregnancy out comes associated with this complication, a history of GDM predisposes women to the future development of type 2 diabetes mellitus[14] (T2DM)

The 24-hour glucose profile performed after the diagnosis of GDM clearly distinguishes between low-risk (diet-treated) and high-risk (insulin-treated) for fetal macrodome in GDM pregnancies[15]. The concentration of TNF alpha, leptin and adiponectin

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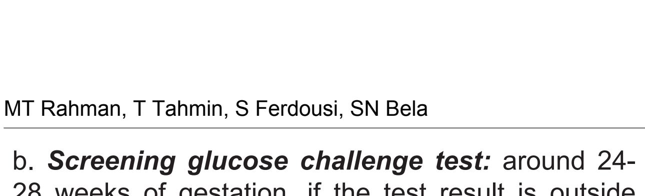
may change studies are required to verify the mechanism of this alteration and wheather the three cytokines can be predictors for GDM at an early stage of pregnancy[16]. There is a high incidence of early postpartum AGR among Chinese women with prior GDM. Beta-Cell dysfunction, rather than insulin resistance or inflammation, is the predominant contributor to the early onset and Consistent AGR after delivery[17]. In a community based study the prevalence of GDM varied in urban,semiurban and rural areas, Age>25years,BMI>25 and family history were found to be risk factors for GDM[18]. There is high incidence of early post partum AGR among Chinese women with prior GDM,Beta cell dysfunctionrather than insulin resistance or inflammation is the predominant contributor to the early onset and consistent AGR after delivery[19]. Psychosocial constructs such as social support and self sufficiency are associated with physical activity and dietary habits. However association with BMI is weak[20].

Pathogenesis of GDM

The exact mechanism of development of GDM is unknown. However the main feature of GDM is increased insulin resistance. Pregnancy hormones and other related factors are thought to interfere with the action of insulin as it binds to the insulin receptor. The interference occurs at the level of cell signaling pathway behind the insulin receptor. Since insulin promotes entry of glucose into cells, insulin resistance prevents glucose from entering the cell properly. As a result glucose remains in the blood stream where glucose level rise. More insulin is needed to overcome this resistance.

Insulin resistance is a normal phenomenon emerging in the second trimester of pregnancy, which progresses thereafter to levels seen in non pregnant patients with type 2 diabetes.

Because glucose travels across the placenta through diffusion facilitated by GLUT 4 carriers the fetus is exposed to higher levels of blood glucose. This leads to increased fetal level of insulin, insulin itself can not cross the placenta. The growth stimulating effect of insulin can lead to excessive growth and a large baby (Macrosomia).



Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor (1) on the cell membrane which in turn starts many protein activation cascades (2). These include: translocation of Glut-4 transporter to the plasma membrane and influx of glucose (3), glycogen synthesis (4), glycolysis (5) and fatty acid synthesis (6).

Source: Wikipedia.

Some risk factors associated with the development of GDM

a. previous diagnosis of gestational diabetes or prediabetes, impaired glucose tolerance or impaired fasting glycaemia.

b. a family history having a first degree relative with type 2 diabetes.

c. Increase Maternal age- a women's risk factors increases as she gets older (especially for women over 35 years of age)

d. ethnic background (those with higher risk factors include African-Americans, Afro-Carribians, Native Americans, Hispanics, Pacific Islanders, and people originating from the Indian subcontinent)

e. overweight, obese or severely obese increases the risk by a factor 2.1,3.6 and 8.6 respectively.

f. previous pregnancy which resulted in a child with a high birth weight(>90th centile, or >4000g (8lbs 12.8 oz)

g. previous poor obstetric history

In addition to this statistics show a double risk of GDM in smokers. Polycystic ovarian syndrome is also a risk factors, although relevant evidence remains controversial. Some studies have looked at more controversial potential risk factors, such as short stature[33].

About 40-60% of women with GDM have no demonstrable risk factor; for this reason many advocate to screen all women.Typically women with gestational diabetes exhibit no symptoms, but some women may demonstrate increased thirst, increased urination, fatigue, nausea and vomiting, bladder infection, yeast infections and blurred vision.

Tests for GDM

a. ***Non Challenge blood glucose tests:*** like Fasting plasma glucose, 2 hour post prandial (after meal) glucose test, Random glucose test if the FBG is above 126mg/dl (7.0mmol/l) and post prandial value above 200mg(11.1mmol/l) and it is confirmed on subsequent day then the diagnosis of GDM is made and no further testing is made.

b. ***Screening glucose challenge test:*** around 24-28 weeks of gestation, if the test result is outside normal limit then after that

c. ***Oral glucose Tolerance test(OGTT):*** after overnight fasting between 8 to 14 hours. During the three previous days the subject must have an unrestricted diet containing at least 150gm carbohydrate per day and unlimited physical activity. The subject should remain seated during the test and should not smoke throughout the test.

d. ***Urinary testing for glucose:*** Women with GDM may have high glucose levels in their urine (glycosuria).

Increased glomerular filtration rates (GFR) during pregnancy contribute to some 50% of women having glucose in their urine on dipstick tests at some point during their pregnancy. The sensitivity of glycosuria for GDM in the first 2 trimesters is only around 10% and the positive predictive value is around 20%.

Complications of GDM

GDM carries risk to both mother and child. This risk is largely related to high blood glucose levels and its consequences. The risk increases with higher blood glucose levels. Treatment resulting in better control of these levels can reduce some of the risks of GDM considerably.

The two main risks of GDM imposes on the baby are growth abnormalities and chemical imbalances after birth, which may require admission to a neonatal intensive care unit. Infants born to mothers with GDM are at risk of being both large for gestational age (macrosomic) and small for gestational age[21,22,23,24].

Macrosomia in turn increases the risk of instrumental deliveries (e.g. forceps, ventouse and caesarean section) or problems during vaginal delivery (such as shoulder dystocia). Macrosomia may affect 12% of normal women compared to 20% of patients with GDM. However, the evidence for each of these complications is not equally strong; in the hyperglycemia and Adverse pregnancy outcome(HAPO) study for example, there was an increased risk for babies to be large but not small for gestational age. Research into complications for GMD is difficult because of the many confounding factors (such as obesity). Labelling a women as having GMD may in itself increase the risk of having a caesarean section[25,26,27,28].

Neonates are also at an increased risk of low blood glucose(hypoglycemia), jaundice, high red blood cell mass(polycythemia) and low blood calcium (hypocalcemia) and magnesium (hypomagnesemia). GDM also interferes with maturation, causing immature babies prone to respiratory distress syndrome due to incomplete lung maturation and impaired surfactant synthesis[29].

Unlike pre-gestational diabetes, gestational diabetes has not been clearly shown to be an independent risk factor for birth defects. Birth defects usually originate sometime during the first trimester (before the 13th week)of pregnancy, whereas GDM gradually develops and is least pronounced during the first trimester. Studies have shown that the offspring of women with GDM are at higher risk of congenital malformations. A large case control study found that gestational diabetes was linked to women with a higher body mass index(>25 kg/ m2). It is difficult to make sure that this is not partially due to the inclusion of women with pre-existent type 2 diabetes who were not diagnosed before pregnancy.

Because of conflicting studies, it is unclear at the moment whether women with GDM have a higher risk of pre eclampsia. In the HAPO study, the risk of pre eclampsia was between 13% and 37% higher, although not all possible confounding factors were corrected.

Prognosis of GDM

Gestational diabetes generally resolves once the baby is born. Based on different studies the chances of developing GDM in a second pregnancy are between 30-84%, depending on the background. A second pregnancy within 1 year of the previous pregnancy has a high rate of recurrence. Women diagnosed with GDM have an increased risk of developing diabetes mellitus in future. The risk is highest in women who needed insulin treatment ,had antibodies associated with diabetes such as antibodies against glutamate decarboxylase, islet cell antibodies and or/insulinoma antigen., women with two previous pregnancies, and women who are obese. Women requiring insulin to manage GDM have a 50% risk of developing diabetes within next 5 years. In some other studies the risk of developing diabetes is 6 years in 50% cases and 70% had diabetes developed after 28 years. In another study in Navajo women , the risk of developing diabetes after GDM is 50-70% after 11 years. Another study showed the risk of diabetes after GDM is 25% after 15 years. In populations with low risk for type 2, in lean subjects and in patients with auto antibodies there is a higher rate of developing type1 diabetes.

In children of women having GDM increased risk of childhood and adult obesity and the risk of

development of type2 diabetes in later life.In a atudy in Jerusalem 410 out of 37962 patients reported to have GDM there was tendency towards more breast and pancreatic cancer among the children[31,32].

Classification:

There are two 2 subtypes of gestational diabetes (Diabetes which began during pregnancy according to Pricilla White):[30]

1. **Type A1:** abnormal oral glucose tolerance test(OGTT) but normal blood glucose levels during fasting and 2 hours after meals; diet modification is sufficient to control glucose levels

2. **Type A2:** abnormal OGTT compounded by abnormal glucose levels during fasting and/ of after meals; additional therapy with insulin or other medications is required.

Treatment:

The goal of treatment is to reduce the risks of GDM for mother and child. Controlling glucose levels can result in less serious fetal complications (such as macrosomia) and increased maternal quality of life.

Counselling before pregnancy (for example, about preventive folic acid supplements) and multidisciplinary management are important for good pregnancy outcomes. Most women can manage their GDM with dietary changes and exercise. Self monitoring of blood glucose levels can guide therapy. Some women will need anti diabetic drugs, most commonly insulin therapy.

Any diet needs to provide sufficient calories for pregnancy, typically 2,000-2,500 kcal with the exclution of simple carbohydrates. The main goal of dietary modifications is to avoid peaks in blood sugar levels. This can be done by using slow release carbohydrate sources. Since insulin resistance is highest in mornings, breakfast carbohydrates need to be restricted more.

Regular moderately intense physical exercise is advised, although there is no consensus on the specific structure of exercise programs for GDM.

Self monitoring can be accomplished using a handheld capillary glucose dosage system. Compliance with these glucometer system can be low. Target ranges advised

Regular blood samples can be used to determine HbA1c levels, which give an idea of glucose control over a longer time period.

If monitoring reveals failing control of glucose levels with these measures, or if there is evidence of complications like excessive fetal growth, treatment with insulin might become necessary.

There is some evidence that certain oral glycemic agents might be safe in pregnancy, or at least, are significantly less dangerous to the developing fetus than poorly controlled diabetes.

Metformin has shown promising results. Treatment of polycystic ovarian syndrome with metformin during pregnancy has been noted to decrease GDM levels. A recent randomized controlled trial of metformin versus insulin showed that women preffered metformin tablets to insulin injection, and that metformin is safe and equally effective as insulin. Severe neonatal hypoglycemia was less common in insulin-treated women, but preterm delivary was more common. Almost half of patients did not reach sufficient control with metformin alone and needed supplemental therapy with insulin compared to those treated with insulin alone, they required less insulin and they gained less weight.

Conclusions

Although GDM is a very serious condition and there is increased risk for mother and child in future to develop obesity, type 2 diabetes. However proper diagnosis, strict glycaemic control, diet modifications with calorie restriction for obese , physical exercise, OHA, Self monitoring blood glucose control etc can reduce the complications in GDM. Efforts should be taken to follow up the patients periodically with HbA1C, FBS, PPS, diet chart and BMI etc to confront this.

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