Gestational Diabetes Mellitus: Generalization and Clinical Treatments

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Abstract. Women of child-bearing age are concerned about multiple risks within the gestational period of which the gestational diabetes mellitus (GDM) is commonly concerned; therefore, generalization of GDM urges to be brought into public view. However, diagnosis criteria and treatment of GDM still lack of standardization and public awareness. GDM first appears after pregnancy due to abnormalities in maternal glucose metabolism which are common complications of pregnancy. The prevalence of GDM is rising worldwide as diagnostic criteria change, and GDM, although it does not have obvious symptoms, can have serious instant and long-lasting complications on both the mother and fetus. Therefore, a detailed guideline is necessary. In order to clarify and synthesize a comprehensive picture of the pathology of GDM and the corresponding treatment options, this article summarizes the background, causes, diagnosis criteria, consequences, and different treatments of GDM. As a result, selective screening associated with oral glucose tolerance tests (OGTT) is the most preferred diagnosis criteria. A collaborative treatment is the most effective approach that causes the least complications.

Keywords: GDM, Diagnosis Criteria, Insulin, Metformin, Glibenclamide.

1. Introduction

The signs of GDM typically occur during the 20-24th weeks of pregnancy. Specifically, placenta supplies nutrients and water for the embryo, and produces a variety of hormones to support pregnancy. The effects of insulin produced by the mother are reduced by these hormones, thus developing contra-insulin effects. Although human pancreas can typically produce more insulin to resist this effect, GDM is developed when the contra-insulin effects overcomes the insulin production of pancreatic islets, especially during later stages of pregnancy when more hormones are produced by placenta [1]. As people's life conditions improve, an increasing number of obese women during childbearing or pre-childbearing age, especially in developed countries, directly causes the increasing diagnosis of GDM. On the other hand, women in developing countries tend to bear children in later stages of their life due to financial concerns, which also increases the risk of GDM. Any woman, or her close relatives, with a history of diabetes (including type 1 and 2) has a higher risk of developing GDM during pregnancy [2]. The rate of detecting gestational diabetes also varies largely depending on racial and ethnic identity: non-Hispanics white women—4.2%, Blacks—4.4%, Hispanics—5.4%, Japanese—5.5%, Koreans—6.7%, Mexicans—7.1%, Pacific Islanders—7.2%, Chinese—7.9%, Southeast Asians—8.8%, Filipinas—9.6%, and Asian Indians—11.1% (from lowest to highest) [3]. However, this result is not exactly accurate since each country has its own criteria of diagnosing GDM.

The health state of both the pregnant women and the offsprings are under tremendous risks due to GDM. Gestational diabetes proposes an increasing risk to diagnosis development diseases for offsprings such as macrosomia, neonatal hypoglycemia and hyperbilirubinemia, and increasing risk of type 2 diabetes for the mother associated with other delivery risks like shoulder dystocia and operative vaginal delivery. An effective diagnosis standard and treatment for gestational diabetes mellitus is in urgency to be developed since GDM is prone to impact both the feminine pregnant safety and health condition of the next generation. This article intends to identify a worldwide

diagnosis criteria, long term consequences for both the mother and offsprings, and possible treatments for GDM considering pregnancy being a special period when some drugs cannot be applied.

2. Diagnosis Criteria

Since contra-insulin effects is a general trend during pregnancy, gestational diabetes mellitus cannot be simply diagnosed based on patients' blood glucose level and insulin level like other types of diabetes. Thus, to reduce the waste of medication resources, the detection of GDM should be focused on patients who have preexisting diabetes or a diabetic family medical history [2].

According to the American Diabetes Association (ADA) and the World Health Organization (WHO), oral glucose tolerance tests (OGTT) are carried out on patients who are suspected of gestational diabetes [2]. OGTT is intended to measure how well the human body can manage an excessive amount of sugar. To perform this test, a concentrated sugar solution is taken by the patient, and blood glucose level is measured as time proceeds [4]. ADA has updated a new procedure and standard for positive diagnosis of GDM in 2015: an OGTT test of 75 grams of sugar is carried out on suspected patients who are not previously diagnosed with diabetes 24—28 weeks into pregnancy after fasting overnight (at least 8 hours). Then, plasma glucose level is measured with different time intervals and compared to the following criteria: fasting serum glucose of 92mg/dl, 1 hour serum glucose of 180mg/dl, and 2 hours serum glucose of 153mg/dl. The patients with plasma glucose level exceeds or equal to the criteria are diagnosed with gestational diabetes. By using this latest diagnostic criteria, the prevalence of GDM can be as high as 18% [5].

3. Long-term Consequences

In addition to the immediate responses of GDM on mother and child, GDM can also have long-term effects.

Although maternal glucose tolerance often reaches the normal level quickly after neonatal birth, GDM patients are more likely to develop type two diabetes (T2DM) at a later time. According to the researches, women who had GDM are 7 times more likely to develop T2DM within ten years after pregnancy. As a result, GDM becomes one of the valid predictors of T2DM.

At the same time, the scientists conducted a comprehensive analysis of the risk of diabetes in offspring of GDM after birth. The researchers followed the offspring of GDM patients (O-GDM) and offspring of background populations (O-BP) until they were 18-27 years old. 21% of O-GDMs have prediabetes or diabetes, compared to only 4% of O-BPs. More seriously, the risk of developing prediabetes or diabetes in O-GDM was 8 times compared to O-BP by excluding various factors that contorted for results. In addition, O-GDM has an approximately 4 times risk of metabolic syndrome compared to O-BP. Finally, O-GDM are 2 times more likely to be overweight in adulthood than those O-BP. As a result, it has shown that GDM has a direct long-term impact on the offspring [5].

4. Treatments

4.1. Lifestyle Modification

Risk of GDM is heterogeneous and BMI is one of the most important factors. Women with BMI greater than 30kg/m^2 have four times the risk of developing diabetes than women of normal weight [6].

Before taking medical treatments, lifestyle changes will be the first option that doctors offer pregnant women to control their blood sugar level. Lifestyle changes include exercise modification and diet modification. The main goal of the modification is not to lose weight but to control the weight in a healthy range.

Physical exercise plays a key role in every wellness plan during pregnancy. Exercise helps lower blood sugar level. GDM can be effectively controlled if women insists on proper exercise during pregnancy [7].

For dietary therapy, specifically, Medical Nutrition Therapy (MNT) is the first step to be taken. A variety of dietary therapies are currently used around the world, but there is no world consensus on which is best. The traditional approach of limiting carbohydrates at the expense of increasing energy from fat sources may not be optimal. Instead, it appears to be more beneficial to consume more complex, low-to-moderate glycemic index carbohydrates and adequate fiber by increasing intake of vegetables and fruits. To assess dietary intake in overweight or obese women (n = 351), who are at high risk for GDM, scientists conducted an experimental analysis using a 3-day diet diary and a diet quality questionnaire during early pregnancy. They calculated eating frequency and nutrient intake to determine dietary patterns. The results showed that a "healthy dietary pattern" of higher intake of vegetables and wheat bread reduced the risk of GDM (adjusted OR 0.27, 95% CI 0.11-0.70) [8]. In order to make MNT work, dietitians must provide dietary advice and nutritional counseling that is easy to understand and use, including healthy food choices and practical guidance that inspire people to change healthy eating patterns. Since GDM can cause long-term effects, not only is a good diet and lifestyle beneficial to avoid the short-term effects of GDM, but consistent improvements are also important for future health [9].

4.2. Insulin

In cases of failure of dietary therapy, medical therapy will be necessary. Insulin is the most well-known choice of medical therapy for treating all types of diabetes.

Normoglycemia is crucial for a safe delivery and healthy mother and offsprings during gestation period, and most GDM patients need insulin to achieve this state. As insulin is injected into human bodies, they will produce insulin antibodies (IA) to respond to the increased amount of insulin. A study consists of pregnant ladies diagnosed with GDM (n=50) are treated with human insulin doses, and their IA levels are measured during the treatment, in their maternal cord blood, and after delivery. Then, the rate of GDM complications are compared between those who tested positive IA (2.9*10^-8mg/dl) and who tested negative IA. As a result of this study, 44% of the ladies tested positive for IA, which means insulin therapy is an effective treatment, and the signs of IA disappeared 6 months after delivery [10].

With the knowledge of insulin being a viable way of treating GDM, maximal tolerated insulin dose (MTD) is developed and considered an effective therapy. As its name implies, MTD is to give patients the highest possible quantity of insulin without causing hypoglycemia. To reach MTD, patients are provided with increased doses of insulin (increased by 5 IU) everyday until slight hypoglycemia is shown, then reduce the doses until normoglycemia is reestablished. In a clinical application of MTD (n=280), maternal mortality rate is only 2%, and cesarean rate varies from 21% to 28% depending on ethnicity. However, offspring from MTD are observed to have an increased probability of establishing vascular complications [11].

In addition to insulin, metformin and glibenclamide are two oral anti-diabetic drugs.

4.3. Metformin

Although variable in efficacy and safety, metformin can be used as an alternative to the treatment of GDM. Since studies of the short-term safety of metformin meet the therapeutic need, metformin is considered as another first-line treatment for GDM in some countries [12].

The safety and efficacy of metformin use during pregnancy was demonstrated by analyzing trial reports of insulin and metformin for GDM in multiple databases. In the experiment, two groups of neonates whose mothers used insulin (n=40) and metformin (n=40) were involved. The occurrence of abnormal births after maternal drug administration is an important consideration in assessing drug safety. The data shows that the rates of preterm births or ruptured births occurring in the two groups are very similar, suggesting that metformin does not differ significantly from insulin in terms of safety.

The glycated hemoglobin value of mothers in the metformin group at 36-37 weeks of pregnancy was significantly reduced, indicating that metformin can also play a good role in controlling blood sugar. So, metformin is often used as a supplemental option to insulin when the amount of insulin is not enough. Also, metformin has been shown to effectively reduce complications of hypertension in pregnancy in patients with GDM. As the injected dose of insulin is reduced, the responses caused by insulin resistance, including endothelial activation and inflammation, are weakened. Though crossing the placenta may result in maternal dystocia, metformin is less likely than insulin to cause fetal hypoglycemia. The reason for this difference is that metformin does not increase the level of insulin secretion. As a result, metformin is a safe and effective treatment for GDM [13].

4.4. Glibenclamide

According to scientific research, glibenclamide is also an effective and stable choice for GDM patients. As an oral hypoglycemic agent that lowers blood sugar levels by stimulating endogenous insulin secretion from pancreatic β-cells, glibenclamide stimulates mobilization of endogenous insulin at lower doses and with a lower incidence of side effects than any other antidiabetic agent available. Glibenclamide is an oral hypoglycemic drug to lower blood sugar level, and its mechanism is to stimulate the pancreatic beta cells to increase insulin levels. It is taken in smaller dosages and has fewer side effects than other antidiabetic drugs.

To demonstrate the efficacy and safety of glibenclamide during GDM in clinical practice, maternal and fetal consequences were evaluated in two groups treated with insulin (n = 45) and glibenclamide (n = 44). Results showed that 77% women using glibenclamide achieved adequate glycemic control, which is close to that of insulin. In the experiment, there were no differences in maternal age and the mode of delivery. In addition, the study showed that the happening rates of maternal weight increase and abnormal births were close among two groups. Finally, after comparing the data of the two groups, the treatment results of glibenclamide during pregnancy were similar to those of women taking insulin, demonstrating that glibenclamide is also effective in the treatment of GDM [14].

4.5. Limitation

All four treatments being discussed have the ability to control glycaemia levels in the mother's body to help delivery, but each of them has different drawbacks.

MNT is a dietary therapy focused on increasing complex carbohydrates and fibers in patients' diet. It can give the patients a healthy lifestyle and does not cause any complications to either the mother or the offspring. However, it can only be applied to early stage GDM patients or associated with medical treatments to control blood glucose levels. Insulin therapy, specifically MTD, can effectively reduce the maternal and infant mortality rates, but it can cause vascular complications for the offspring. Also, the study about insulin effectiveness only has 50 participants, which can cause errors as there are not enough cases being studied. Metformin can control the mother's blood glucose levels, reduce hypertension in mothers, and, most importantly, infants that are treated with metformin during pregnancy do not show hypoglycemia like those treated with insulin. The disadvantage of metformin treatment is that it costs more money than all other therapies. Glibenclamide can well control maternal blood glucose levels to control GDM development, but glibenclamide therapy also causes newborns' hypoglycemia.

5. Prevention

A significant proportion of female diabetes over the world is caused by previous GDM. However, not all of them are aware of getting GDM due to regional diagnosis criteria. A statistical analysis by Cheung and Byth organizes previous studies of GDM in different regions and calculates the relative risks (RR); then, RR is used to calculate population-attributable risks (PAR). Specifically, RR compares the probability of developing T1DM or T2DM between patients who have GDM and patients with a healthy gestation period, and PAR specifies the RRs into each region based on their

diagnosis criteria. As a result, the RR is 95%---most females with GDM will develop T1DM or T2DM---and the PAR varies between 10% to 35%. In detail, the ADA diagnosis criteria mentioned earlier in this article has a PAR between 10% to 23% [15]. Therefore, for the future health of pregnant females, GDM needs to be brought to public attention. Pregnant checks are crucial for the sake of preventing GDM since early stages of GDM can be controlled simply by altering diet. Also, GDM women need to be careful of their diet and lifestyles after delivery to minimize the chance of developing T1DM or T2DM.

6. Conclusion

This article demonstrates the mechanism, diagnosis criteria, consequences, treatments, and prevention of GDM. There is too little attention paid to GDM since there is not even a standard criteria for diagnosis. Majority of people view GDM as a normal hyperglycemia during pregnancy, but it can cause various complications to both the mother and the offspring. In fact, macrosomia caused by GDM can lead to cesarean which can cause the mother's death if not managed well. To retrench the limited medical resources, selective screening should be applied as the first stage of diagnosis---women with preexisting diabetes or diabetic family medical history. Then, OGTT is carried out on those suspected of GDM, and their blood glucose levels from OGTT are compared to ADA diagnosis criteria. The knowledge of long-term consequences is crucial for the patient and her family, so they understand what they are facing. Four common treatments, diet, insulin, metformin, and glibenclamide, are discussed and compared. All of them are useful to control blood glucose levels, but all of them have potential flaws. Association of the treatments is commonly used in clinical trials. Most importantly, a correct mindset toward GDM is beneficial for the public health in general since it can influence two generations of people. In the future, GDM and other feminine diseases are necessary to be brought into public views and be considered equally serious as other diseases instead of simply a pregnancy disorder, so the overall health of the society and the next generation will both improve.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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