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Genetic and Environmental Factors in Gestational Diabetes Mellitus: A Review

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Abstract

Gestational diabetes mellitus [GDM] is a condition associated with glucose intolerance first diagnosed during pregnancy. Over the years, there has been an increase in prevalence of women with gestational diabetes; resulting to increasing studies on this type of diabetes. Genetic studies on GDM, reveals its association with genes such as Glucokinase- *GCK*, Variable Number Tandem Repeats on Insulin gene-*INS-VNTR*. Certain factors predisposes an individual to GDM, which includes: Body Mass Index or body weight, ethnic group/race, age. Various complications such as macrosomia, hyperinsulinemia, nerve palsies and fetal mortality has been associated with GDM. While it has been observed that most women with GDM, later developed postpartum type 2 diabetes. Presently, the management and treatment involves diet modification, exercise and use of hypoglycaemic agents.

Keywords: Body Mass Index [BMI]; Gestational Diabetes Mellitus [GDM]; Insulin Receptor Substrate -1 [IRS-1]; Insulin resistance.

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1. Introduction

Gestational diabetes mellitus [GDM] is any form of glucose intolerance first diagnosed during pregnancy [1]. This indicates that women with gestational diabetes were never diagnosed of having diabetes before conception. As a result of this, clinicians recommend Oral Glucose Tolerance Test [OGTT] for women during gestation. This test is normally conducted between the 24-28th week of gestation [2]. A threshold of 135mg/dL [7.5mmol/L] was recommended by the American College of Obstetricians and Gynaecologists, especially in women with high risk of GDM [1].

A previous study in 1990, showed the prevalence of GDM to occur in about 10% of all pregnant women [3]. Various reviews show an increased prevalence of GDM from 10-100% with respect to the race or the ethnic group, thereby posing a major concern to health practitioners around the globe [4-8]. With this increasing prevalence, certain questions arises; such as: who is at a risk of gestational diabetes? Are there gene(s) involved in predisposition to this condition? What effect(s) does environmental factors have on gene expression?

2. Evidences for genetic factors

There are various genetic factors which could predispose a woman to gestational diabetes, these factors include: ethnic group, health history, previous delivery of a macrosomic baby and the presence of certain genes.

2.1. Ethnic group

Individuals belonging to races or ethnic groups such as Hispanic-America, Native-America, South-East Asia, Africa and Australia are more predisposed to gestational diabetes than others. This deduction was due to observed increase in prevalence of GDM among these races [9-11]. A study conducted in 1999 on the Canadian population [Quebec], showed that there was a high prevalence of GDM among Cree women [12].

A further study was conducted in the same year on 394 Cree women and 788 non-natives. Their results showed that 11.4% of Cree women had GDM when compared with 5.3% of non-native women [13]. The researchers in [13] attributed this difference to be due to high obesity among Cree women. Thereby increasing their predisposition to GDM. Therefore, within these ethnic groups some women who seem “normal” might have an undiagnosed pre-diabetes before gestation.

2.2. Health and gestational history

Women with previous diagnosis of prediabetes are highly predisposed to gestational diabetes, when compared to women with normal plasma glucose level; This is as a result of higher than normal plasma glucose level, which is not high enough to be refered to as diabetes [2, 14]. Therefore, in the presence of certain environmental factors such as hormonal interactions during gestation; gestational diabetes could result. An individual with first degree parents having diabetes, could be predisposed to GDM [2]. Thereby increasing the likelihood of inheriting polymorphic or mutant genes (*PPARγ2-PRO12Ala*,*INS VNTR* and *GCK* genes) which could predispose such an individual to either type 1, type 2 or gestational diabetes [11].

Alernatively, previous delivery of a baby with a weight of 4.0kg or more increases the risk of gestational diabetes[2]. Macrosomia resulting from GDM, indicates that there was an over-expression of certain placental hormones [15]. Therefore, there is a probability that such hormones would be overexpressed in subsequent pregnancies. In addition, women with history of GDM in a previous pregnancy are at a higher risk of developing it again in subsequent pregnancies.

2.3. Gene/genotypic analyses

Researches are being carried out to observe the association between genes responsible for predisposition to type 1, type 2 diabetes and GDM [11, 16]. Some of the genes studied include: *INS VNTR, HLA-DQB1* and *GCK* genes.

2.3.1. INS VNTR, PPARγ2 and HLA-DQB1 genes

The insulin hormone is coded for by the *INS* gene. Study on the *INS* gene showed the presence of a variable number tandem repeat about 0.5kb upstream of the *INS* gene. The VNTR was found to be about 15bp long, consisting of the sequence ACAGGGGTCTGGGG, though there could be slight variation in the repeat sequences [16]. It has been observed that the *INS* gene expression is determined by the number of polymorphic VNTR repeats [17]. Some studies have shown the possibility of an association between *INS* gene, type 1 and type 2 diabetes [18-20]. Besides the *INS* gene, another gene which has been studied is the *HLA-DQB1* gene; which plays an important role in immune system regulation and an increased risk of type 1 diabetes [11]. Furthermore studies on this gene have shown that women with a family history of diabetes had a high frequency of polymorphic *HLA-DQB1* alleles responsible for diabetes [11]. The *PPARγ2*- (peroxisome proliferative-activated receptor-gamma -2) is a transciption factor, which regulates lipid storage and glucose metabolism [21]. It influences the expression of certain genes necessary for glucose metabolism by binding to specific promoter-regions of these genes [21]. An example of such polymorphism is *PPARγ2-PRO12Ala* [22].

A study was carried out in 2004, to observe the genotypic differences in diabetic gene (*INS VNTR, HLA-DQB1* and GAD65Ab) association between Arabian and Scandinavian women with GDM. In this study they observed a total of 500 women with GDM (400 Scandinavian and 100 Arabian) and 550 women non-GDM (428 Scandinavian and 122 Arabian). The results of their research showed that Arabian women with GDM were 50% more insulin resistant when compared with Scandinavian women of the same BMI; while the Scandinavian women with GDM had a higher frequency of *HLA-DQB1* gene than the corresponding Arabian women [11]. In addition, they observed that both groups of women with GDM had a higher frequency of GAD antibodies (GAD65Ab) than women with normoglycaemia. Futhermore, their study on Insulin gene variable number tandem repeat *–INS VNTR* and peroxisome proliferator-activated receptor-gamma 2 *–PPARγ2-PRO12Ala* polymorphism in both groups (between the GDM and non-GDM women) revealed no significant differences in the frequencies of these genes. These findings implies that predisposition to GDM could be detected by testing for GAD65Ab. While the differences in frequencies for insulin resistance and *HLA-DQB1,* were due to racial differences which might have resulted from variations in gene pool between the two populations. In addition,

this also deduces that there would be a higher prevalence of type 1 diabetes and GDM among the Scandinavian population, when compared with the Arabian population.

2.3.2.Glucokinase [GCK] gene mutations

A Glucokinase enzyme catalyzes the phosphorylation of glucose to glucose-6-phosphate. In addition to this, it plays an important role in carbohydrate metabolism, by acting as a glucose sensor for the pancreas, liver and brain [23]. The glucokinase enzyme is coded for by the *GCK* gene. Therefore, a mutation in the *GCK* gene would result in an alteration in the glucokinase enzyme produced [24].

A study was conducted in the United Kingdom by [25]; they observed 15 GDM women, from which some had GDM in previous pregnancies. Their results showed that 12 (80%) of 15 subjects used had mutations in their glucokinase genes. The following mutations were found K161+2del15, N180K, R191W, Y215X and L288-1G-> A. The mutation in L288-1G->A is a frameshift mutation, while that of Y215X was found to be a nonsense mutation. Contrary to these findings, a similar research carried out on the Brazilian population yielded a completely different result. In which they screened 200 women (100-: GDM with good glycaemic control and 100-: non-GDM) for mutations in the *GCK* gene [26]. They observed that only 13 women out of the 200 (6.5%) subjects used for the study had *GCK* gene mutations. They detected a new mutation-: intron3 (c.43331A>G), while the others found were intron 6 (c.47702T>C, rs2268574), intron 9 (c.48935C>T, rs2908274) and exon 10 (c.49620G>A, rs13306388). Therefore, the researchers in [26], concluded that there were no associations between the mutations they observed and GDM. Considering these two findings, the reason for the observation in [25], could have been as a result of the sample size (15 subjects); with respect to that of [26] in which 200 subjects were utilized. In addition, the *GCK* gene mutations associated with GDM could vary from one population to the other resulting from variations in the gene pool which could be responsible for the disparities observed.

3. Environmental factors influencing gestational diabetes

The phenotypic expression observed is often times determined by the genotypic composition, but there are instances in which the phenotypic expression of a gene is modified by certain environmental factors. With respect to this, the expression of GDM in certain women could be influenced by some environmental factors. Such as:

3.1. Body weight

A pre-gestation Body Mass Index [BMI] of about 25kg/m^2 or more increases predisposition to GDM when compared to women with normal BMI [2, 27]. In [28] a study was carried out to observe the effect of pregestation BMI and risk of GDM using 1644 women. They observed that women with BMI >29kg/m^2 were at a very high risk of GDM, when compared to women with low, normal or overweight BMI [28]. They further observed that women who had a pregestation weight gain of ≥10kg in adulthood, were three times more likely to develop GDM compared with women who gained ≤2.5kg. Therefore, this implies that pregestation body weight has an influence on gestational body weight, which invariably increases the risk of GDM; unless lifestyle and

diet management is advised and ensured. In addition, studies have proven the probability of a relationship between gestational weight gain in early pregnancy and gestational diabetes. A study conducted by [29], compared the weight gain in the early pregnancies of two groups of women (345-women with GDM and 800-control); they observed that women with high rate of gestational weight gain in early pregnancy are at a high risk of GDM [29]. Another research was done by [9], in which they observed the correlation between BMI and GDM taking into consideration 5 races (Asian, Filipina, Hispanic, white non-Hispanic and African-American). They observed that at normal BMI (22-24.9kg/m^2), there was a GDM prevalence of about 8.0 and 9.9% among the Asian and Filipina women; when compared with the other races, which had a prevalence of >8.0% in only overweight and obese women with BMI >28kg/m^2. A critical evaluation of these findings, indicates that pregravid increase in BMI is a high risk for GDM, especially if such an individual is genetically predisposed to GDM or belongs to a high risk ethnic group. The molecular explanation for this is still being studied. Researchers believe that an accumulation of fatty acid (overweight and obese individuals) can trigger insulin resistance [30]. It has been found that in the presence of ATP and Long chain Acyl CoA synthetase, fatty acids can be converted to Long chain Acyl CoA and Diacylglycerol. Which has the ability to activate serine/threonine kinases. These kinases phosphorylates Insulin Receptor Substrate-1 (IRS-1), leading to a decrease in phosphatidylinositol (P13-kinase) activation complex. Thereby, preventing the insulin=IRS-1 complex, resulting to insulin resistance and GDM [31-33]. Therefore, this explains why increase in BMI would invariably lead to increased pre-disposition to GDM.

3.2. Age

Women who are above 25 years and still reproducing are highly predisposed to GDM, which occur as a result of decreased production of insulin due to increasing age [2, 10].

3.3. Hormonal factors

During pregnancy the foetus derives its glucose from the mother through the placenta; this action by the foetus could result to maternal hypoglycaemia. Therefore, in order to prevent this, certain placental hormones undergo several interactions, which is directed at preventing hypoglycaemia. Some of these interactions could result to insulin resistance in the mother. One of such Studies have shown that overexpression of Tumor Necrosis Factor-Alpha (TNF-α), which is a placental hormone; would lead to serine phosphorylation of placental insulin receptors (IRS-1), thereby altering it [34]. Normally, IRS-1 forms a complex with phosphatidylinositol (P13) kinase, which then facilitates the addition of insulin molecule to the insulin receptor substrate. Unfortunately, the serine phosphorylation of the IRS-1, hinders the formation of the enzyme=substrate complex; leading to the inability of insulin to bind to the substrate known as Insulin Resistance [35].

4. Resultant effects of GDM on foetal and neonatal health

Maternal insulin resistance would result in the inability of cells to absorb glucose for energy metabolism, storage and an increased concentration of plasma glucose. Thereby, leading to an increase in the concentrations of triglycerides, fatty acids, cholesterol and protein in circulations [36]. These increased plasma glucose,

triglycerides and amino acids could be passed to the foetus through the placenta [37]. Which invariably requires an increased secretion of insulin by the foetus; in order to facilitate the absorption and utilization of glucose, triglycerides and amino acids. Consequently, these results in abnormal increase in growth and fat deposits; leading to macrosomia, perinatal mortality, polycythemia and other birth defects [27,38,39].

In addition, maternal overexpression of placental hormones (Leptin and TNF-α), would result in the activation of phospholipase A2 (which is a lipolytic enzyme that catalyzes the conversion of alpha linolenic acid -ALA to docosahexanoic acid –DHA, a type of omega-3-polyunsaturated fatty acid). Therefore overexpression of placental hormones, leads to accumulation of omega-3-polyunsaturated fatty acid in the foetus. Resulting in excessive foetal adiposity known as Macrosomia [40].

Alternatively, inability of maternal cells to absorb glucose would result to over utilization of fat for energy metabolism; thereby leading to increased production of ketones. Which if when passed to the foetus, could cause Diabetes Ketoacidosis; resulting in foetal mortality [41-42].

In addition, post-natal studies have shown that children from GDM mothers, had a higher BMI compared to their peers; which is due to over-accumulation of glucose and fat deposits during intra-uterine growth [27].

5. Resultant effects of GDM on maternal health

Women with GDM are more likely to undergo caesarean section, due to the macrosomic size of the baby [43]. Often times, women with GDM develop type 2 diabetes after delivery [44, 47]. A postnatal study conducted between 1971 and 2003, involved observing and monitoring 5470 GDM women and 783 non-GDM subjects [45]. The result of the observation showed that 7.2% of the GDM subjects developed postpartum type 2 diabetes compared with 2.0% of the control. This implies that women who develops GDM during gestation are more likely to develop postpartum type 2 diabetes.

6. Treatment and management of GDM

Just like other types of diabetes, GDM is presently being treated and managed through diet modification, exercise and pharmacological methods.

6.1 Diet modification

Nutrition therapy should be encouraged and ensured through the help of a dietician or a nutrition counselor. This helps to guide the indivdual in the type and quantity of food intake with respect to BMI [2]. Studies have shown how restriction of daily calorie to approximately 25kcal/kg can reduce hyperglycaemia in obese women having BMI 30kg/m^2 or more [46]. Thereby, reducing the predisposition to developing GDM. In addition, diet modification could also help delay or prevent postpartum type 2 diabetes.

6.2 Exercise

In addition, exercise or intensive lifestyle has been found to delay the onset of type 2 diabetes in women with GDM [47]. As recommended by [44], an individual with a history of GDM should undergo about 30 minutes exercise daily in order to enhance glucose metabolism and weight loss. A study by [47] showed a 50% reduction in the progression of GDM to type 2 diabetes in GDM subjects who were involved in a combination of an intensive lifestyle and metformin; when compared with GDM subjects administered with placebo. The result from this study explains that intensive lifestyle would help GDM individual maintain a normal BMI, thereby reducing the risk of developing type 2 diabetes.

6.3. Pharmacological methods

The treatment of GDM using pharmacological methods need to be handled with high importance. As any suitable hypoglycaemic agent must not be able to pass through the placenta to the foetus, in order to prevent foetal hyperinsulinemia [44]. In addition, the hypoglycaemic agent should be used with caution, by ensuring regular/daily monitoring of blood glucose levels, in order to avoid an overdosage [2]. Various studies have been carried out on the different types of hypoglycaemic agents, which were suitable in managing the GDM; but further studies needs to be done to ascertain whether it passes through the placenta. One of such studies is that of [48], in which they observed the effectiveness of insulin aspart in maintaining a normal postprandial blood glucose in GDM, when compared with other types of insulin derivatives (regular exogenous human insulin and endogenous human insulin). Despite the effectiveness of the insulin aspart, its effect(s) on the foetus was not stated or ascertained.

7. Summary and prospects

Increasing prevalence of GDM in high-risk population and its expression among low-risk; indicates its need for utmost attention. Other forms through which the condition can be managed and treated should be explored, taking into consideration the health of the foetus. In addition, early detection and screening among high-risk population, would be a guide to monitoring, managing and preventing the condition.

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