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Review

Gestational Diabetes - The Epidemic of the Century

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Abstract

Gestational diabetes mellitus is diagnosed in the second and third trimester of pregnancy. Although the exact etiology of this condition is still unknown, it is thought to be related to a hormonal imbalance that impacts insulin sensitivity and pancreatic β-cell malfunction. This review provides an overview of the latest reports on the epidemiology, pathogenesis, diagnosis and treatment of GDM based on the literature. All the literatures and potential information are collected from the genuine data base such as Pub Med, Scopus Web of Science, etc. The results from the review revealed that nearly 1/6th pregnancies are associated with hyperglycemia among which 84% are diagnosed under GDM. Nearly 366 million people are affected with diabetes mellitus with an increased in the gestational diabetes worldwide. GDM is more common in India because of decrease in physical activity, alteration in the diet and also due to obesity. In conclusion, this review found that GDM can be addressed as a multifactorial and complex process that can evolve from various mechanisms. Free-of-cost GDM screening and proper treatment for maternal health care can be a significant step towards diabetes care. Half of the women are not aware of their glucose intolerance until they have their index pregnancy and glucose screening. Therefore, there is need to create awareness of this condition with early intervention, proper treatment, diet and multidisciplinary care programs. It can help to reduce the risk of GDM and complications in the general residents and high-risk individuals and promote long-term health.

Keywords: Gestational Diabetes, White's classification, Risk factors, Insulin Therapy.

INTRODUCTION

Diabetes mellitus (DM) is one of the major chronic illnesses that threatens majority of the population for years. This requires self-management, education and support that minimize the complications related to this disease. Apart from the glycemic control, diabetic care and management is required to prevent the risk factors associated with that disease [1–3].

Pregnancy is considered as a "window" for a women's health, because the physiologic changes that occur during this time act as a natural "stress test" for the body [4]. Therefore, majority of the women consults a physician for their preventive healthcare guidance. The maternal nutritional status of a woman directly influences the health of the offspring throughout their lifespan[5]. One among this change is glucose intolerance that leads to hyperglycemia. This is called as gestational diabetes mellitus (GDM) [6].

Gestational Diabetes Mellitus (GDM) is defined as "diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation"[7]. Yet the pathophysiology is found to be mysterious, but it may be linked with the hormonal imbalances that affect the insulin sensitivity and pancreatic β-cell dysfunction[5,8]. The anti-insulogenic hormones like estrogen, progesterone, human placental lactogen, cortisone and growth hormone increase in second and third trimester of pregnancy causing glucose intolerance in minor population among the pregnant women leading to GDM.

In recent years, nearly 1/6th pregnancies are associated with hyperglycemia among which 84% are diagnosed under GDM. Nearly 366 million people are affected with diabetes mellitus with an increased in the gestational diabetes [9]. International diabetes federation have framed a theme for the year 2017, "women and diabetes" to create awareness among the pregnant women on how they care for their new born. In 2013, the International Diabetes Federation states that 16% of the births worldwide are affected with GDM. During the early stage of pregnancy, the most common demand of fetus is increased in glucose for maternal secretion of estrogen and progesterone leading to hyperinsulinemia [5].

Due to the more severe fetal and maternal complications resulting from such diabetes mellitus antedating pregnancy, in 2013, the WHO has divided hyperglycemia in pregnancy as follows:

- Diabetes in pregnancy: Pre-gestational diabetes (PGD) or pregnancy occurring in a women with known diabetes and overt diabetes (diabetes first detected during pregnancy)
- Gestational diabetes mellitus.

CLASSIFICATION OF DIABETES IN PREGNANCY

The diabetes in pregnancy has classified based on two types, epidemiologically and clinical purpose. In 1949, the White's classification was developed which was named after Dr. Priscilla White, she has categorized the gestational diabetes patients from "A" (more favorable) to "F" (less favorable) on the basis of various factors such as age of gestation, diabetes duration, metabolism and vascular complications. This White's Classification (table 1) was modified several times till 1980. In 1965, the first revised White's Classification was modified by changing vascular complications to "D" and adding class "R" indicating the presence of proliferative retinopathy. In 1972, the white's classification was further updated in which, GDM was included in class "A" and class "D" was subdivided into five categories.

The latest modification applied to the White's classification includes addition of GDM as a distinct separate class and deletion of class "E" and "G". Later, The American College of Obstetricians and Gynecologists (ACOG) proposed another classification for GDM, proposing the presence or absence of metabolic complications [10–12].

Table 1: The White's Classification [12]

CLASS	ONSET (AGE)	DURATION	INSULIN	CRITERIA
A_1	Any	Any	No	Gestational Diabetes
A_2	Any	Any	Yes	Gestational Diabetes
B	>10	<10	Yes	Benign retinal and renal findings
C	10-19	10-19	Yes	Age of onset 10-19 years or duration 10-19 years
D	<10	>10	Yes	Age onset <10 or duration >10
F	Any	Any	Yes	Nephropathy (500mg/day of protein)
R	Any	Any	Yes	Proliferative retinopathy
RF	Any	Any	Yes	Retinopathy and nephropathy
T	Any	Any	Yes	Renal transplant patient
H	Any	Any	Yes	Cardiovascular disease

EPIDEMIOLOGY

The prevalence of GDM was found to be 1-14%, it depends on various factors such as, area of population, screening strategies and diagnostic methods. Therefore, the prevalence was found to be 5%, 3-7%, 2-6% respectively among the United Kingdom, US and Europe. Africa, Asian, Indian and Hispanic women were found to increase in the prevalence of gestational diabetes. GDM is more common in developing countries like India and Pakistan because of decrease in physical activity, alteration in the diet and also due to obesity [13]. Indians are considered to be at the highest risk for gestational diabetes. Several criteria are responsible for the increase risk of GDM in India such as high burden, rising prevalence of diabetes, constraint of resources and high rate of

deliveries (27 million/year) [14–16]. By the end of 2025, the prevalence of GDM would expect to increase from 62% to 79.4% that becomes the second biggest population worldwide. The prevalence of GDM is nearly <5% in countries such as Pakistan, Belgium, Denmark, Estonia, Ireland, South Korea, South Africa and UK. Whereas, < 10% in Italy, Turkey, Brazil, United States, Morocco and Australia, 20% in Bermuda and Nepal [3,17–19].

ETIOLOGY

Type 2 Diabetes Mellitus (T_2DM)

GDM is most commonly a forerunner of T_2DM. Women with GDM have a sevenfold risk for T_2DM for several years compared to women with normal glucose tolerance (NGT) during pregnancy. Longitudinal studies longer than 10 years indicate that more than 25% of GDM will develop T_2DM. Women with GDM display insulin resistance before and after pregnancy as in predisposed T_2DM subjects. GDM is found to carry more T_2DM risk alleles. A genome-wide association study performed from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study shows that among the susceptibility genes, variants of glucokinase (GCK) and Transcription Factor 7L2 Gene (TCF7L2) loci are associated with higher glucose levels during oral glucose tolerance tests in pregnant women [20–22].

Type 1 Diabetes Mellitus (T_1DM)

Auto-immune diabetes may also be considered as etiology of GDM. The prevalence of auto-immune markers of type 1 diabetes mellitus (T_1DM) is between 0.98 and 1.47% in women with GDM. It predicts later development of T_1DM in these women but not necessarily. In some studies, positive islet cell autoantibodies need to be tested in GDM deserves further studies. Autoimmunity was associated with poor pregnancy outcomes such as Fetal death, Preterm delivery and Microsomia [23, 24].

Genetic susceptibility

Genetic and epigenetic processes are responsible for the development of GDM. The confirmatory gene factors in GDM patients includes, epigenetic alterations such as, DNA methylation, histone modification, microRNA (miRNA) gene silencing. Impairment of pancreatic islet β-cell function may lead to genetic pre deposition in some individuals [25–27].

A type of hereditary DM responsible for 5% of all diabetes cases is Maturity-Onset Diabetes in the Young (MODY). The changes in glucose level are caused due to physiological changes which are` disrupted by monogenic mutation with subsequent metabolic changes typical of diabetes. The onset of symptoms is usually before the age of 25 due to pancreatic β-cell dysfunction. 14 variations of MODY have been identified till date. The relationship between mutations of MODY & GDM are listed in table 2. The most common MODY type and gene mutations are:

- MODY 3: Hepatocyte Nuclear Factor 1 Alpha (HNF1A)
- MODY 1: Hepatocyte Nuclear Factor 4 Alpha (HNF4A)
- MODY 2: Glucokinase (GCK)
- MODY 5: Hepatocyte Nuclear Factor 1 Beta (HNF1B)

Although there are few more MODY are responsible for metabolic actions such as, ATP binding cassette subfamily C member 8 (ABCC8), β-lymphocyte kinase (BLK), carboxyl ester lipase (CEL), neurogenic differentiation 1 (NEURO1), paired box 4 (PAX4), pancreatic duodenal homeobox (PDX), and others [28–30].

Table 2: Mutations of MODY and GDM

MODY Type	Gene	Full Name	Mutation Influence on Pathophysiology
Most common mutations accounting for 70–90% of MODY cases			
MODY 3	HNF1A[28]	Hepatocyte nuclear factor-1 alpha	Gradual beta-cell dysfunction, reduced insulin production and progressive hyperglycemia
MODY 1	HNF4A[25,27]	Hepatocyte nuclear factor-4 alpha	Progressive beta-cell dysfunction, fetal macrosomia, hyperinsulinemic hypoglycemia
MODY 2	GCK[31–34]	Glucokinase	Disrupted glucose sensing and hyperglycemia
MODY 5	HNF1B[25,27]	Hepatocyte nuclear factor 1B	Dysfunctional pancreatic development, suppressed cytokine signaling and formation of kidney cyst

MODY mutations of lower prevalence			
MODY 4	IPFI/PDX1[28,30]	Insulin promoter factor/pancreatic duodenal homeobox	Pancreatic agenesis, beta-cell development and defective insulin secretion
MODY 13	KCNJII[25,27,35]	Inward-rectifier potassium channel, subfamily J, member 11	Congenital hyperinsulinism
MODY 12	ABCC8(25,27,36)	ATP binding cassette subfamily C member 8	Congenital hyperinsulinism, disrupted biogenesis and insulin trafficking of KATP channels
Other GDM mutations			
	CAPN10[26,37]	Calpain-10	Dysfunction of cell metabolism and signal transduction and elevated fasting glucose levels
	ADRB3[38,39]	β3-adrenergic receptor	Decreased insulin excretion, disrupted thermogenesis and lipolysis
	INSR[38,39]	Insulin receptor	Disrupted metabolism of β-cell and elevated glucose levels
	IRS1[38,39]	Insulin receptor substrate 1	Dysfunction of intracellular signaling and increased insulin resistance
	GLUT4/SCLA4[38,39]	Insulin-sensitive glucose transporter protein 4/solute carrier family 2, member 4	Progressively increasing insulin resistance
	PC-1	Plasma cell membrane glycoprotein 1	Increased insulin resistance

Other factors

Some factors like ethnicity and races may be the origin of GDM onset. GDM may result from interaction between genetic and environmental risk factors. Old age, obesity and high fat diet represent some important non-genetic factors [40].

PATHOPHYSIOLOGY

In normal pregnancy, maternal tissues become progressively insensitive to insulin. This is caused by hormones from the placenta and other obesity and pregnancy related factors. The main glucose disposable sites in human body is skeletal muscle and adipose tissue. In normal pregnancy, insulin-mediated whole-body glucose disposal decreases by 50% and in order to maintain a euglycemic state, the woman must increase her insulin secretion by 200%-250%[41, 42]. GDM develops when the pregnant woman is not able to produce an adequate insulin response to compensate for this normal insulin resistance. GDM is observed in obese as well as in lean women. However, the pathophysiology behind the disease is believed to differ between these groups. In obese women, the pathophysiology is primarily characterized by the pregnancy-induced insulin resistance being amplified by elevated pre-pregnant insulin resistance level. The elevated insulin resistance level is a known factor in the metabolic syndrome[43]. In lean women, the same factors seem to play a role but a defect in the first phase insulin response contributes to a larger extend. These defects culminate in a disruption of the action of insulin in maintaining glucose levels, resulting in maternal hyperglycemia. Glucose is transferred via the placenta to the fetus. Maternal hyperglycemia stimulates a foetal hyper insulinaemia to counter the excess placental glucose transfer. The high insulin level in the fetus stimulates growth which results in foetal macrosomia (birth weight over 4000 g) [41–44].

RISK FACTORS

Modifiable risk factor

The modifiable risk factors include overweight, obesity, pre-pregnancy Body Mass Index (BMI), metabolic syndrome, nutritional diet, Polycystic Ovary Syndrome (PCOS), Pre-Eclampsia. Apart from these conditions, other factors such as environmental stress, use of antidepressant and psychotropic medications, smoking and poor sleep are included in the modifiable risk factors [3, 8, 18, 45].

Obesity plays an important role in GDM over 20% of females are at higher risk when compared to non-obese females. As a result, it causes increase in morbidity and mortality of the fetus which can be rectified by early diagnosis to achieve the desired pregnancy outcome [46].

Non-modifiable risk factor

The non-modifiable risk factors include maternal age, gravidity, parity, ethnicity, genetics and family history of hyperglycemia [8, 9]. GDM can cause increase the risk of cesarean operative vaginal delivery, macrosomia, shoulder dystocia, neonatal hypoglycemia and hyperbilirubinemia. If a woman is affected with GDM, they are at high risk for developing T2DM and in future their child would develop obesity [46].

Socioeconomic Risk Factors

Climate, geographical location, education and socio-economic status have direct impact on human health. Mostly pregnant women are not aware of the risk factors and the complications associated with them. A survey reported that the socio-economic status and gestational diabetes are inversely proportional to each other. Therefore, to improve the efficacy of GDM treatment, promoting health education combined with government support to patients is an important component of prenatal care [6,8,47].

DIAGNOSIS

Gestational diabetes is one of the common metabolic problems during pregnancy, therefore it needs an accurate diagnosis of gestational diabetes mellitus such as high plasma glucose first identified during pregnancy, is critical to the care of pregnant women. The screening of GDM is done by assessing the clinical risk factors or by the 50g glucose challenge test (GCT). The diagnosis of GDM is made by 75g or 100g oral glucose tolerance test (OGTT). The World Health Organization (WHO) provides guidelines for numerous communicable and non-communicable diseases. GDM is no exception and due to the worldwide reach [48].

Diagnostic criteria in India

The Diabetes in Pregnancy Study group in India (DIPSI) has developed practical usable recommendations for diagnosis of GDM in the community. This guideline has been recognized by the Ministry of Health, Government of India, the Federation of Obstetrics and Gynecological Societies of India (FOGSI) and the Association of Physicians of India (API) [48–50].

Testing for GDM is recommended twice during antenatal care. The first testing should be done during first antenatal contact as early as possible in pregnancy. The second testing should be ideally done during 24-28 weeks of pregnancy if the first test is negative. If women present beyond 28 weeks of pregnancy, only one test is to be done at the first point of contact. A single step is recommended by measuring plasma glucose 2 hours after ingestion of 75g glucose irrespective of the last meal (Fasting or No fasting). In the absence of available laboratory facilities, a standardized glucometer may be used to evaluate plasma glucose. A glucose level of ≥ 7.8 mmol/L is the cut off for diagnosis of GDM. It is called DIPSI test [51, 52].

COMPLICATIONS

GDM is characterized by hyperglycemia diagnosed during pregnancy, caused by or compounded with underlying mechanisms such as genetic predisposition, insulin resistance, and chronic inflammation. Although the condition is usually transient, it is a risk factor for the development of T2DM later in life and may also lead to long-term adverse effects in both mother and offspring [53, 54].

Maternal complications

Hyperglycemia may damage endothelial cells, which can result in vascular dysfunction associated with hypertension. Because of this, it is suggested that GDM increases the incidence of hypertension during pregnancy and the postpartum period. Both diabetes and hypertension are risk factors for the development of pre-eclampsia, a disorder which affects between 3% and 5% of pregnancies worldwide which is characterized by high blood pressure and proteinuria [54–56].

Fetal complications

The developing fetus has a limited ability to produce glucose; therefore, it derives most of its glucose from maternal blood. Maternal glucose crosses the placenta, while maternal insulin does not. Pedersen hypothesis stated that maternal hyperglycemia results in fetal hyperglycemia. Hence it results in hypertrophy of fetal pancreatic islet cells resulting in insulin hyper secretion [51, 53, 55].

Neonatal Complications

Neonatal complications include possible asphyxia, hypoglycemia, kernicterus, jaundice, bacterial infections, neonatal respiratory distress syndrome (NRDS), birth trauma, shoulder dystocia and injury to the brachial plexus. Neonatal hypoglycemia occurs as a result of the abrupt cessation of the maternal source of glucose

at birth. This is exacerbated by fetal hyperinsulinemia due to GDM and requires extensive treatment and care if the hypoglycemia persists [53, 55, 57].

PHARMACOLOGICAL TREATMENT

INSULIN THERAPY[58–60]

Initiation Criteria

Insulin therapy is recommended when self-monitored glucose values consistently show abnormalities, with specific thresholds indicating the need for intervention. These thresholds often include fasting glucose levels exceeding 95 mg/dL and postprandial levels surpassing 120 mg/dL for 2 hours or over 140 mg/dL for 1 hour.

Safety and Effectiveness

Insulin, encompassing regular, NPH, Lispro (Humalog) and Aspart (Novolog) stands as the gold standard for GDM treatment. The safety and efficacy of insulin make it a cornerstone against which other pharmacological interventions are compared.

Insulin Remodeling

Ongoing efforts in insulin research have led to the development of insulin lispro, which demonstrates superior management of postprandial hyperglycemia compared to regular human insulin without an increased risk of hypoglycemia.

Glargine Use

Although limited data exist on glargine use during pregnancy, insulin therapy has demonstrated benefits including a reduction in operative deliveries and birth trauma.

Dosage and Administration

Insulin dosage is weight-based, ensuring a conservative approach to prevent hypoglycemia. The regimen typically involves morning and evening doses with a portion of the total daily dose administered before breakfast and the remainder split before dinner and at bedtime.

ORAL HYPOGLYCEMIC AGENTS

Table 3: Oral hypoglycemic agents

NAME OF THE DRUG	DRUG PROFILE	SAFETY CONSIDERATIONS
METFORMIN [60,61]	Metformin, a well-established oral hypoglycemic agent for diabetes outside of pregnancy that has gained acceptance as an alternative or adjunct to insulin during gestation. **MOA:** By improving insulin sensitivity, metformin enhances glucose tolerance during pregnancy, potentially reducing the physiological rise in insulin resistance associated with gestation.	Metformin may be safe during pregnancy, potentially reducing the risk of miscarriage and GDM development.
GLYBURIDE [60,62]	Glyburide has emerged is second generation sulfonyl urea derivative **MOA:** It is a potent stimulator of pancreatic insulin secretion after short-term administration, an additional mechanism of action during long-term administration is to decrease the resistance of muscle and liver to the action of insulin [63].	Glyburide, categorized as a Class C medication in pregnancy, has a safety profile indicating a low incidence of adverse effects, with hypoglycemia reported in 1-5% of cases.
ACARBOSE [62]	Acarbose not extensively studied in pregnant women with diabetes show efficacy in reducing postprandial glucose excursions in GDM. **MOA:** It acts by delaying the digestion of carbohydrates; acarbose slows glucose	Poor systemic absorption and potential transplacental passage of acarbose necessitate further evaluation for safety during pregnancy.

	absorption, resulting in a reduction of postprandial blood glucose concentrations [64].	

NON-PHARMACOLOGICAL MANAGEMENT [65]

Pre-pregnancy Counseling

Women with type 1 or type 2 diabetes require comprehensive pre-pregnancy counseling to maintain optimal blood glucose levels. For those already on treatments, intensive monitoring is imperative from the onset of conception.

GDM Monitoring Throughout Pregnancy

Monitoring frequency in GDM varies throughout pregnancy with intensified monitoring after the 28th week and a shift to weekly monitoring after the 32nd week. Continuous glucose monitoring devices though available, may be reserved for high-risk pregnancies due to specialized training requirements and cost considerations.

Ensuring Treatment Effectiveness

Regular monitoring of glycemic control is paramount for the success of GDM treatment, whether through a structured meal plan or pharmacological interventions. Adjustments to insulin dosage or other interventions should be made based on monitoring outcomes.

CONCLUSION

Gestational diabetes is a chronic disorder that requires continues medical care, self-management and support to prevent acute complications to reduce long term complications. The management of GDM is crucial and involves various strategies such as insulin therapy, oral hypoglycemic agents, pre-pregnancy counseling and continuous monitoring. It gives the rising prevalence, proactive measures in healthcare, public awareness and research are essential to address this growing health issue. Understanding and addressing the multiple risk factors, along with effective management strategies are pivotal in ensuring better outcomes for both mother and child during and after pregnancy.

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