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GESTATIONAL DIABETES MELLITUS: COMPLICATIONS AND MANAGEMENT

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ABSTRACT

Gestational diabetes mellitus(GDM), which is defined as a glucose intolerance of any degree with onset or first recognition during pregnancy, is currently the most common medical complication in pregnancy. GDM affects approximately 14% of pregnancies worldwide, accounting for approximately 18 million births annually. The GDM occurs when hormonal changes during pregnancy lead to insulin resistance, resulting in inadequate insulin production and impaired glucose metabolism. Risk factors include obesity, overweight, advance maternal age, family history of diabetes, PCOS and type 2 diabetes mellitus. Diagnosis and screening of GDM is performed using one step method of 75g oral glucose tolerance test(OGTT) and two step method of 50g glucose challenge test and a 100g OGTT should be performed. GDM is increase the risk of short and long term complications in both maternal and fetal. Mother with GDM are at risk of developing macrosomia, preeclampsia, preterm birth and termination of pregnancy via Caesarean section. GDM increase perinatal complications including hypoglycemia, hypocalcaemia, polycythemia, respiratory distress syndrome, congenital malformation and

offspring obesity and postpartum Type 2 diabetes mellitus. The primary treatment for GDM are diet and proper exercise. Insulin, metformin and glyburide can be used intensify the treatment.

KEYWORDS: Gestational diabetes; Risk factors, Maternal complications; Fetal complications

INTRODUCTION

Gestational diabetes mellitus is a common complication of pregnancy characterized by spontaneous hyperglycemia. According to the International Diabetes Federation's 2017 estimate, maternal hyperglycemia affects one in every six pregnancies globally, with approximately 14% of pregnancies worldwide being affected by diabetes mellitus, resulting in approximately 18 million births annually.[1] In most cases, this hyperglycemia is due to impaired glucose intolerance resulting from pancreatic β-cell dysfunction on a background of chronic insulin resistance.[2] The first scientist to describe diabetes in pregnancy was Bennewitz in Germany in 1824, with subsequent case series in the United Kingdom and the United States reporting high perinatal mortality rates in women with diabetes in pregnancy.[3] In 1964, O'Sullivan and Mahan recognized that gestational diabetes mellitus is defined as hyperglycemia first detected during pregnancy, occurring in the second or third trimester.[4] Diagnosis is usually performed using an oral glucose tolerance test (OGTT), although non-fasting glucose challenge tests (GCT) are used in some parts of the world to screen women requiring a full OGTT.[6] Gestational diabetes mellitus increases the risk of long-term complications in both mother and infant, including impaired glucose metabolism, cardiovascular disease, and diabetes in childhood and adulthood. It is also associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia or other birth injuries, preeclampsia, perinatal depression, preterm birth, and stillbirth. Gestational diabetes mellitus has been associated with an increased risk of pregnancy-induced hypertension (PIH) and an increased rate of cesarean delivery.[5] Unfortunately, there is currently no widely accepted treatment or prevention strategy for gestational diabetes mellitus, except for lifestyle intervention (diet and exercise) and occasionally insulin therapy, which is only of limited effectiveness due to the insulin resistance that is often present. While emerging oral anti-diabetics, such as glyburide and metformin, are promising, concerns remain about their long-term safety for the mother and child.[6]

PATHOPHYSIOLOGY

Pregnancy

⇩

Increased the placental hormone with anti – insulin effect such as lactogen, estrogen, progesterone and cortisol in the maternal circulation due to lack of insulin resistance

⇩

Increased blood glucose level in maternal, which leads maternal hyperglycemia

⇩

High level of glucose crosses the placenta enter into the fetal circulation

⇩

Which stimulates the release of insulin by fetal pancreatic β cells and starts to respond to hyperglycemia.

⇩

Resulting fetal hyperinsulinemia[7]

DIAGNOSIS

All pregnant women who do not have type 1 or type 2 diabetes undergo screening for gestational diabetes between 24 and 28 weeks of gestation.[8]

METHOD	TEST	GLUCOSE THRESHOLDS
One step Method	75-g Oral Glucose Tolerance Test (OGTT)	Fasting 8-12 hours Fasting ≥ 92 mg/dl 1hour ≥ 180 mg/dl 2hour ≥ 153 mg/dl
Two step Method	50-g Glucose Challenge Test (GCT)	Non Fasting GCT> 140 mg/dl
	100-g OGTT (Oral Glucose Tolerance Test)	Fasting 8-12 hours Fasting ≥ 92 mg/dl 1 hour ≥ 180mg/dl 2 hour ≥ 155 mg/dl 3 hour ≥ 140 mg/dl

RISK FACTORS OF GDM

- Over Weight Or Obesity
- Maternal Age (Or) Advanced Age
- Pre Diabetes
- Genetic Factors

- Not Being Physically Active
- Polycystic Ovarian Syndrome
- Family History Of Type 2 Diabetes
- Ethnicity

COMPLICATION OF GDM IN MATERNAL AND FETAL

MATERNAL COMPLICATIONS

1. Macrosomia

Macrosomia is a persistent complication in gestational diabetes mellitus. The term macrosomia or large for gestational age (LGA) is used to express the notion of excessive fetal growth. Macrosomia is defined as a birth weight exceeding 4000g or above the 90th percentile for gestational age.[10] Approximately 15-45% of babies born to GDM mothers can have macrosomia. Maternal hyperglycemia and maternal overweight are independent risk factors for fetal macrosomia. Fetuses with macrosomia in diabetic pregnancies develop central deposition of subcutaneous fat in the abdominal and interscapular areas, resulting in big shoulders and a decreased head-to-shoulder ratio, and notably higher body fat.[9]

Macrosomia-Related Complications

Maternal Complication[9]

The process of vaginal birth becomes increasingly complex when the size of the baby is larger than average. In cases of macrosomia, the fetus may become lodged in the birth canal, necessitating the use of instrumental delivery or even an emergency cesarean section. Additionally, macrosomia deliveries carry a heightened risk of laceration and tearing of vaginal tissue, as well as potential tearing of the perineal muscle between the vagina and anus.

Fetal Complications[9]

- Premature birth may occur as a result of early induction of labor before 39 weeks (approximately 9 months) of gestation or premature rupture of membranes, which poses a risk of preterm delivery.
- Shoulder dystocia is one of the most severe consequences of vaginal delivery in macrosomic babies, and is associated with birth trauma.
- Neonatal jaundice is a common occurrence in macrosomic neonates due to their high oxygen demand, which causes increased erythropoietin and subsequent polycythemia.

This results in an increase in bilirubin (a byproduct of red blood cells), leading to neonatal jaundice.

- Hypoglycemia at birth is the most common metabolic disorder in neonates of mothers with gestational diabetes mellitus (GDM).
- The high blood sugar levels of women with GDM can damage the developing organs of the fetus, leading to congenital anomalies.

2. Preeclampsia

Preeclampsia and gestational diabetes mellitus (GDM) are two significant complications that can arise during pregnancy. The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines preeclampsia as the onset of hypertension after 20 weeks of gestation.[11]

Preeclampsia is diagnosed in women who present with new onset hypertension and proteinuria during the second half of pregnancy. Insulin resistance at 22-26 weeks' gestation is a significant independent predictor of preeclampsia.[13] Both preeclampsia and GDM are challenging and common issues in antenatal care, with preeclampsia responsible for approximately 16-18% of maternal perinatal deaths and up to 40% of fetal and neonatal deaths.[11] Factors associated with occurance of PE in women with GDM Pre- pregnancy BMI, Gestational weight gain, Time of GEM occurrence, Blood glucose level, Advance maternal age, Chronic hypertension, PCOS.[12]

The occurrence of preterm birth and fetal growth restriction (FGR) has been observed in women with gestational diabetes mellitus (GDM) and preeclampsia (PE). Furthermore, there is an elevated rate of respiratory distress syndrome among infants born to mothers suffering from both GDM and PE.[13]

Mechanism

The pathophysiology of PE involves two stages, early insufficient trophoblast invasion leads to complete spiral artery remodeling, which causes placental ischemia and oxidative stress. The diseased placenta progressively releases elevated amounts of anti-angiogenic factors that cause maternal inflammation and vascular endothelial dysfunction, and finally lead to PE. The mechanism of GDM affecting the occurrence of preeclampsia.[12]

3. Preterm Birth

Gestational diabetes mellitus (GDM) is an autonomous risk factor for preterm birth (PB), which is characterized by the delivery of an infant prior to the completion of 37 weeks of gestation. The primary contributors to the incidence of PB in women with impaired carbohydrate metabolism are pre-gestational diabetes mellitus (PGDM), type 1 diabetes (T1D), and type 2 diabetes(T2D). Glycemic imbalance in GDM patients can lead to acute fetal distress, jeopardizing the well-being of the unborn. In such cases, emergency fetal extraction via C – section becomes necessary to ensure the immediate rescue of the fetus from distress.[14]

Risk Factors For Premature Birth Women With DM[14]

In Mother Side

- Hypertension is correlated with a twofold increase in the likelihood of developing preeclampsia and an elevated risk of premature delivery.
- The existence of obesity and gestational diabetes mellitus (GDM) constitutes a significant risk factor for preterm birth.
- Diabetic nephropathy, a microvascular complication of diabetes mellitus, serves as a crucial predictor of preterm birth development.

In Fetal Side

- Fetal macrosomia, the large size of the fetus causes an overgrowth of the uterus, which is one factor that initiates labor.
- Polyhydramnios in GDM is excessive urination of fetus due to hyperglycemia. For now, infections that damage the amniocytes contribute to active fluid secretion. Overgrowth of the uterus leads to premature outpouring of amniotic fluid or early beginning of labor.
- Diabetic fetopathy-deformity of a fetus in women with uncompensated GDM leads to the need for early delivery and increase the frequency of PB.

FETAL COMPLICATIONS

1. Hypoglycemia

- The etiology of hypoglycemia in neonates born to mothers with gestational diabetes mellitus (GDM) is short-term hyperinsulinism. This condition inhibits the usual counter-regulatory responses, including glycogenolysis, gluconeogenesis, lipolysis, and beta

oxidation of fatty acids, which are responsible for compensating for the loss of glucose supply from the placenta and increases peripheral glucose utilization.[15]

- The prevention and management of hypoglycemia in neonates born to mothers with GDM involves pre-feed blood glucose monitoring and early and frequent breastfeeding. For mildly symptomatic infants with low blood glucose levels, sustained breastfeeding or formula supplements should be attempted first, provided a satisfactory clinical response is obtained.[10] However, some infants may have hypoglycemia that cannot be managed with breastfeeding alone and will require IV glucose supplementation. This should be provided at a constant rate of infusion (3-6 mg/kg per hour) to avoid rebound hypoglycemia.[10]

2. Hypocalcaemia

- Hypocalcaemia is a medical condition characterized by a total serum calcium level of less than 8 mg/dL (2mmol/L) or an ionized calcium concentration of less than 4.4 mg/dL (1.1mmol/L) in any case of birth weight. During the third trimester of pregnancy, calcium is transferred from the maternal blood circulation to the fetal circulation via the placenta.[16]
- Hypocalcaemia in the infants of diabetic mothers may occur due to hypomagnesemia in the mother and infants, which is caused by an increase in maternal urinary excretion of magnesium during pregnancy.[17] Hypomagnesaemia can lead to functional hypoparathyroidism in the infants. The increased maternal calcium resulting from maternal hyperparathyroidism is passed to the infants via the placenta, which suppresses fetal PTH synthesis and impairs PTH response to postpartum hypocalcaemia.[16]

3. Polycythemia

- Polycythemia is a condition that frequently occurs at birth in infants born to diabetic mothers. This condition poses an increased risk for hyperviscosity, renal vein thrombosis, cardiac failure, and necrotizing enterocolitis in affected infants. Additionally, hyperbilirubinemia, resistant hypoglycemia, hypoglycemia, and hypomagnesemia may also be associated with this condition in infants.[18]
- The development of polycythemia in infants is thought to be caused by fetal hyperinsulinemia and elevated erythropoietin (EPO) levels due to intrauterine chronic hypoxia. However, no consistent correlation between plasma EPO levels and polycythemia has been reported in humans or animals.[18] The mechanism behind this condition involves a decrease in transplacental oxygen transport to the fetus and an

increase in fetal utilization due to fetal hyperinsulinism. These factors may lead to fetal hypoxia and an elevated level of fetal EPO.[10]

4. Hyperbilirubinemia

- Infants born to pregnant women with diabetes during pregnancy are at an elevated risk of developing hyperbilirubinemia in comparison to normal infants. This is due to an increase in red blood cells, which subsequently leads to an increase in bilirubin.[19]
- In cases of macrosomia, neonates experience a heightened demand for oxygen, resulting in increased erythropoiesis and ultimately polycythemia. The breakdown of these cells leads to the production of bilirubin, which can result in neonatal jaundice.[9]

5. Respiratory Distress Syndrome

- Preterm birth women with diabetes mellitus the possibility of developing RDS in new Borns from mothers with GDM in higher than the general population of the same gestational terms. Matrnal hyperglycemia, Fetal hyperglycemia develops, which cause Fetal hyperinsulinism inhibit the lung surfactant synthesis. The lung surfactant insufficiency can result in RDS.
- Insufficient control of carbohydrate metabolism in the fetal lungs persists as a morpho-functionally immature state even after 34 weeks of pregnancy.[14] The potential sources of RDS in newborns of mothers with GDM include an increased risk of preterm birth and elective cesarean section delivery due to macrosomia. Elective cesarean section delivery increases the risk of RDS through the mechanism of retained fetal lung fluid.[15]

6. Congenital Malformation

Maternal diabetes has deleterious effects on the embryonic development and significantly elevates the risk of congenital malformations in humans. The congenital malformations linked with diabetic pregnancies manifest prior to the seventh week of gestation. Diabetic embryopathy can impact any developing system in the fetus, including the central nervous system(anencephaly, spinabifida, microcephaly, haloprosencephaly), skeletal system(caudal regression syndrome, sacral agenesis, limb defects), renal system(renal agenesis, ureteric abnormalities,hydronephrosis), cardiovascular system(transposition of the great vessels, ventricular septal defects, arterial septal defects, cardiomyopathy) and gastrointestinal system(duodenal atresia, anorectal atresia, small left colon syndrome). Gestational diabetes

mellitus (GDM) is associated with a substantial risk for holoprosencephaly, upper/lower spine/rib defects, and anomalies in the renal and urinary systems.[20]

7. Offspring Obesity

Obese women with gestational diabetes mellitus (GDM) exhibit a higher level of insulin resistance in maternal hyperglycemia, which can lead to maternal hypertriglyceridemia and fetal hyperglycemia. This, in turn, can result in increased birth size and adiposity, as well as hyperinsulinemia in the fetus. Such conditions can lead to excessive fetal growth associated with macrosomia and increased adiposity. Furthermore, the excessive adiposity at birth can have long-term effects on the offspring's adiposity.

8. Postpartum Type 2 Diabetes Mellitus

Gestational diabetes mellitus (GDM) is a recognized risk factor for postpartum type 2 diabetes mellitus (T2DM) in women's health. Any degree of dysglycemia during pregnancy predicts a proportional risk of progressing to T2DM in the future, with GDM representing the most severe element along this continuum (i.e., the highest gestational glycemia and the highest risk of T2DM).[23] The postpartum weight management maybe an effective prevention stratergy that can lower the risk of postpartum T2DM. Factors Associated With Occurrence Of Postpartum T2DM in Women With GDM, obese women, BMI of 25-29.9 and >30kg/m^2, Fasting glucose level 100-109.9 and >110mg/Dl, Age 35-39 year, Family history of diabetes, hypertension and insulin treatment.[24]

Pathophysiology

Women who develop GDM have a chronic β-cell defect that first becomes clinically apparent through the antenatal hyperglycemia that arises due to the insufficiency of their compensatory response. Importantly, in addition to underlying the presentation of GDM in pregnancy, this β-cell defect is ultimately responsible for their development of Type2 diabetes mellitus in the future. Specifically, women with GDM exhibit deterioration of β-cell function in the years after their pregnancy that is apparent even with in the first year postpartum while their glucose tolerance may remain in the normal range. Over time however this deterioration of β-cell function drives their progression from normal glucose tolerance to pre-diabetes and ultimately to T2DM.[23]

TREATMENT

Non-Pharmacological Management

✓ **Life style and behavioral management.**

Upon diagnosis, treatment commences with medical nutrition therapies, physical activity, and weight management, contingent upon the pre-gestational weight, as delineated in the section below on pre-existing type 2 diabetes. Additionally, glucose monitoring is implemented with the objective of achieving the targets recommended by the Fifth International Workshop Conference on Gestational Diabetes Mellitus.

- Fasting glucose <95mg/dl(5.3mmol/l) and either
- One hour postprandial glucose<140mg/dl(7.8mmol/l)
- Two hour postprandial glucose <120mg/dl(6.7mmol/l)

✓ **Physical Activity**

Exercise intervention can lead to enhancements in glucose control and a decrease in the necessity to initiate insulin or insulin dose requirements. The types of effective exercise, whether aerobic, resistance, or both, and the duration of exercise, ranging from 20-50 minutes per day, 2-7 days per week, of moderate intensity, exhibited heterogeneity.

✓ **Nutritional Treatment**

Nutritional recommendations are essential for women to attain normoglycemia, optimal weight gain, and proper fetal development. In the case of women with gestational diabetes mellitus (GDM), carbohydrates are the most crucial macronutrient, and their excessive consumption can lead to hyperglycemia. The diet should constitute 40-50% of the energy requirement, not less than 180g/day, and primarily comprise starchy foods with a low glycemic index. Increased intake of plant protein, lean meat, and fish, along with reduced consumption of red and processed meats, can be beneficial in improving insulin sensitivity.[25]

Pharmacological Treatment

Patients who are unable to attain glycemic targets through adherence to a proper diet and elimination of dietary errors ought to receive pharmacological treatment. The majority of studies suggest that insulin therapy is the most secure form of treatment, and orally administrated drugs (OAD) should only be considered if the patient refuses insulin therapy or if it is not readily available.

✓ **Insulin Therapy**

The administration of insulin therapy is conducted through the functional intensive insulin therapy (FITT) model, utilizing subcutaneous injections. The utilization of human insulin during pregnancy has been demonstrated to be safe. Randomized trials have confirmed the safety of aspart and determine analogs, while observational studies have shown the safety of lispro and glargine analogs, including their passage across the placenta. In women with normal pancreatic function, insulin production is adequate to meet the demands of physiological insulin resistance and maintain normal glucose levels. However, in women with diabetes, hyperglycemia may occur if treatment is not appropriately administered.

Types of Insulin

❖ Human insulin

❖ Regular insulin

Regular insulin is identified to human insulin and it is used as meat time insulin to cover postprandial hyperglycemia. Its time to onset is about 30 minutes, the effect is in 3 hours and effect ends at about 8 hours.

❖ **Human Insulin Inhalation (Nasal Insulin)**

The administration of human insulin via inhalation, also known as nasal insulin, is comparable in potency to insulin lispro on a unit-for-unit basis. Its onset of action occurs within 15 minutes, with a peak action time of approximately 50 minutes. The duration of its effect is approximately 2 hours. It is important to note that the use of inhaled human insulin carries a boxed warning for the potential occurrence of bronchospasms in patients with chronic lung disease.

❖ **Rapid-Acting Insulin Analogues**

An additional analogue of human insulin is derived from saccharomyces cerevisiae, a species of yeast. Aspart should be administered 5-10 minutes prior to a meal and may be administered via multiple subcutaneous injections or insulin pumps. Its peak action time is 40-50 minutes, and its duration of action is 3-5 hours. Notably, insulin aspart elicits a lower incidence of hypoglycemia compared to regular insulin.[26]

Sulfonylureas

Sulfonylureas are recognized to traverse the placenta and have been linked to elevated neonatal hypoglycemia concentrations. The levels of glyburide in umbilical cord plasma are

roughly 50-70% of maternal levels. In meta-analyses and systematic reviews, glyburide was found to be associated with a greater incidence of neonatal hypoglycemia, macrosomia, and increased neonatal abdominal circumference compared to insulin or metformin.

Metformin

Metformin is a commonly utilized medication during the early stages of pregnancy for patients diagnosed with polycystic ovarian syndrome. Additionally, it is administered during the second and third trimesters as a drug treatment for gestational diabetes mellitus (GDM) in cases where lifestyle modifications have failed to achieve desired glycemic goals.[27]

Glyburide

Glyburide, a second-generation oral sulfonylurea, elicits insulin secretion from pancreatic beta-islet cells, thereby inducing cellular membrane depolarization. It has been demonstrated to be more effective than first-generation agents and boasts a superior safety profile. Furthermore, the transfer rate of glyburide from mother to fetus or vice versa, two hours after dosing, is a mere 0.26%. The extensive plasma protein of glyburide is transported by p-glycoprotein, and the majority of the fetal load is returned to the mother. When administered at equivalent dosages, the plasma concentration of glyburide is approximately 50% lower in pregnant women than in non-pregnant subjects.[28]

CONCLUSION

GDM is one of the most common complications of pregnancy and increasing global prevalence. In 21st century, GDM imposes a major challenge for healthcare professionals. Change in lifestyle and dietary patterns, as well as lack of understanding pregnancy complications have increased the occurrence of GDM in pregnant women. Diagnosis GDM is important because prenatal complications and stillbirth risk are reduced by treatment. Age, obesity, diabetes in the family history, ethnicity, macrosomia, and perinatel complications has been identified as risk factors for GDM. Gestational diabetes mellitus (GDM) is associated with a range of complications and risks for both mothers and their offspring. The interaction between maternal hyperglycemia, fetal hyperinsulinemia, and other factors contribute to these complications, which can have significant short-term and long-term health implications. Management and prevention strategies for these complications often involve close monitoring, appropriate medical interventions, and postpartum weight management for mothers with GDM. Proper treatment is crucial for GDM management. Non-pharmacological

approaches, exercise, and balanced nutrition are initial strategies. Pharmacological options like insulin and certain oral medications are available for more severe cases.

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