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Review Article

A clinical update on the molecular pathogenesis of gestational diabetes mellitus and its consequences

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ABSTRACT

Gestational diabetes mellitus (GDM) is becoming more common all over the world, mainly to an increase in maternal obesity. There have been a number of approaches to screening for and diagnosing GDM described, however there is no consensus on which methods are the most effective. For the mother, developing fetus, and children born to mothers with GDM, GDM poses severe short and long-term health hazards. Macrosomia, shoulder dystocia, delivery trauma, and hypoglycemia in the immediate postpartum period are all short-term dangers for the fetus. Increased rates of childhood and adulthood obesity, as well as a higher cardio metabolic risk, are long-term hazards for offspring born to women with GDM. More investigations on the aetiology and underlying mechanisms of gestational diabetes and its complications on the long-term health of offspring are needed to offer a foundation for creating effective therapies during this important period with the goal of promoting lifelong health and well-being.

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1. Introduction

India has long been known as the world's diabetic capital, and gestational diabetes mellitus (GDM) is a much worse problem in India than it is elsewhere. It is commonly accepted that diabetic women, especially pregnant and lactating women, are among the most vulnerable.¹ India is the world's most populous democratic country, with 16 percent of the world's population. Unfortunately, with 45,000 maternal deaths in 2015, India has the highest maternal mortality rate in the world. It is one of six countries responsible for half of all maternal deaths worldwide.² In comparison to other Asian nations; the prevalence of GDM is significantly higher in the Indian population.³ Diabetes is a major health problem in India, with prevalence rates

ranging from 14% in urban regions to 13.2% in rural areas. In India, T2DM affects an estimated 62 million people, with that number expected to climb to 79.4 million by 2025. It is unsurprising that the incidence of GDM is increasing at the same time as the prevalence of diabetes.⁴ In the year 2013, 6 million pregnant women in India were diagnosed with hyperglycemia, with GDM accounting for 90% of the cases. GDM is usually asymptomatic and is most often discovered by standard screening during pregnancy. The guidelines developed by the International Association of Diabetes and Pregnancy Study Group (IADPSG) were implemented in 2010 and have subsequently gained universal recognition. However, other studies suggest that it may raise the risk of GDM.⁵ GDM affects about 5 million women in India each year. According to the literature, pre-diabetes and diabetes impact nearly six million newborns in India alone, with GDM accounting for 90% of cases.⁶

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2. The Molecular Pathophysiology of GDM

The biology of GDM isn't completely understood. Insulin resistance is a major feature of the underlying pathology; in general, pregnancy triggers a number of maternal adaptation processes that help the embryo develop and grow in a metabolically healthy way. Reversible expansion of maternal insulin secretion and increasing insulin resistance are two key pregnancy adaptation processes that happen as a result of functional changes and increased β cell mass.⁷ The placenta is important in the development of temporary insulin resistance during pregnancy, which returns to normal immediately after delivery. Insulin resistance is caused by the placenta's release of hormones, cytokines, adipokines, and other chemicals into the maternal circulation.⁸ Human chorionic gonadotropin (hCG), human placental lactogen (hPL), and human placental growth hormone (hPGH) are all secreted by the placenta and bypass the regular hormonal regulation circuits.⁹ Hepatic gluconeogenesis and lipolysis are boosted by placental lactogen and growth hormone, and maternal insulin-like growth factor I (IGF-1) levels rise in response to higher growth hormone levels. Placental growth hormone (PGH) is a key regulator of maternal insulin like growth factor I (IGF-I).¹⁰ Increased levels of IGF-I, IGF-II, IGF-IR, and IGF-IIR mRNA in the placenta are linked to foetal macrosomia.¹¹ The maternal circulation has an increase in pregnancy related hormones such as estrogen, progesterone, cortisol, and placental lactogen,¹² increased insulin resistance is also present. This normally occurs between the 20th and 24th week of pregnancy.

In addition, adipocytokines, such as leptin, adiponectin, tumour necrosis factor- (TNF-), interleukin-6, resistin, visfatin, and apelin, are produced by adipose tissue.¹³ These play a role in glucose homeostasis, which can lead to insulin resistance in a pregnant woman.¹⁴ GDM affected pregnant women have higher glucose levels and lower levels of various amino acids, creatinine, and glycerophosphocholine.¹⁵ Changes in glucose, amino acids, glutathione, fatty acids, sphingolipids, and bile acid metabolites in the amniotic fluid of GDM compared to non GDM fetuses were also described in mid-gestation in the amniotic fluid of GDM fetuses.¹⁶ Maternal hyperglycemia is linked to structural abnormalities in the placenta, including increased placental weight, increased angiogenesis (chorangiogenesis), and delayed villous maturation.¹⁷ The placenta secretes glucose, proteins, and lipoproteins into the umbilical cord plasma. Some of these compounds aid in the development and growth of the foetus.¹⁸ As a result, foetal macrosomia may be caused by abnormal function and expression of glucose transporter proteins (Glut proteins) in the placenta, which results in excessive maternal to foetal glucose transfer.¹⁹ Glucose levels were found to be higher in foetal amniotic fluid samples taken from GDM mothers.¹⁵ The increased expression of GLUT-1, GLUT-4, and GLUT-9 in term

human placentas from both GDM and PGDM mothers corresponded with foetal birth weight, suggesting the involvement of GLUT proteins in intrauterine foetal growth facilitation.²⁰

2.1. Insulin and fetal growth

Insulin regulates foetal growth as an anabolic hormone.²¹ Foetal hyperglycemia and hyperinsulinemia are caused by maternal hyperglycemia, which activates the foetal mitogenic and anabolic pathways in growing muscles, connective tissues, and adipose tissue.²² Overgrowth is caused by foetal hyperinsulinemia, whereas intrauterine growth retardation (IUGR) is caused by foetal insulin insufficiency.²³ The amniotic fluid of foetuses from mothers with PGDM or GDM had high insulin levels.²⁴ Carpenter et al. found a link between high amniotic fluid insulin levels in the second trimester and foetal macrosomia in 247 hyperglycemic pregnant women.²⁵ As a result, maternal glucose intolerance during pregnancy may have an impact on foetal insulin production as early as the second trimester. Indeed, diabetes women's foetuses have pronounced β -cell mass within the pancreatic islets in the second trimester, compared to nondiabetic women's foetuses, and release more insulin after acute glucose exposure with increasing gestational age, the difference in pancreatic β -cell mass between diabetic and nondiabetic foetuses becomes increasingly prominent.²⁶

The insulin-secretory activity of pancreatic β -cell has been found to be reflected in plasma C-peptide, which could be employed as a diagnostic for foetal hyperinsulinemia.²⁷ Total insulin, C-peptide, and free insulin levels in umbilical vein plasma have all been found to be elevated in diabetic pregnancies. Two months after delivery, DubÉ et al. discovered a link between cord blood C-peptide levels and maternal insulin, C-peptide, and insulin sensitivity indices values.²⁷ The levels of C-peptide in the cord blood of 18 pregnant women with GDM and 23 pregnant women with normal glucose tolerance (NGT) were measured. When GDM mothers offspring were compared to control nondiabetic mothers' offspring, higher cord blood glucose levels were found. In general, maternal insulin, fasting C-peptide, insulin sensitivity, interleukin-6, body mass index, and newborn weight were all linked with cord blood C-peptide levels in both groups.²⁷

2.2. Factors affecting fetal growth in diabetic pregnancies

The factors that affect foetal growth in diabetes mothers are depicted in Figure 1. Insulin resistance is mediated by pregnancy related hormones such as estrogen, progesterone, cortisol, and cytokines, as well as additional growth hormones released by the placenta and circulating in the maternal circulation, such as hPGH and placental

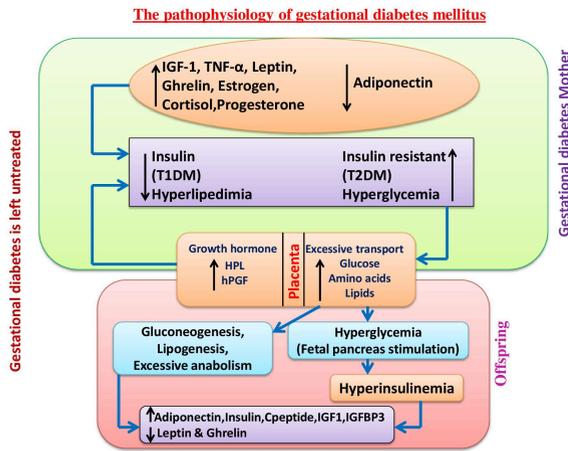


Fig. 1: The pathophysiology of GDM

lactogen. Adipocytokines, such as leptin, adiponectin, and TNF- α , are also produced by adipose tissue and may play a role in insulin resistance. Insulin resistance causes glucose intolerance and hyperglycemia in most people. As a result, the placenta alters and the fetus accumulates too much glucose, amino acids, and lipids. Hyperinsulinemia is produced by the fetus in response to maternal hyperglycemia, which lowers foetal blood glucose levels while increasing foetal fat tissue and promoting development. Furthermore, PGH promotes foetal gluconeogenesis and lipogenesis, resulting in increased foetal growth.

3. Long-term Complications to the Mother

3.1. Type 2 diabetes mellitus (T2DM)

Women who have had previous GDM have been demonstrated to have a significantly higher chance of developing T2DM.²⁸ When compared to non-GDM pregnancies, GDM patients have a 7-fold increased risk of T2DM, according to a systematic evaluation of 20 research papers.²⁸ According to a population-based study, 18.9% of women with previous GDM got T2DM within 9 years of the index pregnancy, while only 2% of women without GDM had T2DM (2.0 percent). The rate of T2DM development increased in the first nine months after delivery, with 3.7 percent of patients acquiring T2DM during that time frame.²⁹

3.2. Cardiovascular disease

GDM increases the risk of metabolic syndrome and cardiovascular disease after childbirth. Central obesity, hypertension, insulin resistance, and dyslipidemia are all risk factors for metabolic syndrome.²⁹ Several studies have found a link between GDM and the incidence of maternal cardiovascular morbidity.³⁰ Women with a history of GDM are more likely to develop cardiovascular risk factors as hypertension, dyslipidemia, obesity, and metabolic syndrome. Specifically, GDM was revealed to be an independent risk factor for noninvasive diagnostic procedures, uncomplicated cardiovascular events, and cardiovascular hospitalizations in long-term mothers.³¹ Women with GDM showed considerably greater levels of vascular endothelial dysfunction indicators than women who had normal pregnancies; according to Bo et al. GDM mothers have a higher risk of developing cardiovascular disorders than normoglycemic mothers, according to the authors.³² Furthermore, another study found a dose response effect between glucose levels during pregnancy and postpartum atherosclerotic morbidity when there is modest glucose intolerance.³³

3.3. Obesity

A comprehensive metaanalysis looked at the link between childhoods elevated BMI and maternal diabetes, and showed a robust link between prenatal mother diabetes exposure and increased childhood BMI.³⁴ Obesity rates after in utero exposure to GDM were as high as 4.9 percent in diet controlled GDM and 7.8 percent in diet-uncontrolled GDM, according to Abokaf et al. Obesity rates in non-GDM women’s offspring were as low as 1.8 percent.³⁵ In other cohorts, a link between GDM and offspring obesity has been found.³⁶

3.4. Ophthalmic disease

GDM has also been linked to an increased risk of long-term ophthalmic morbidity. When compared to controls,

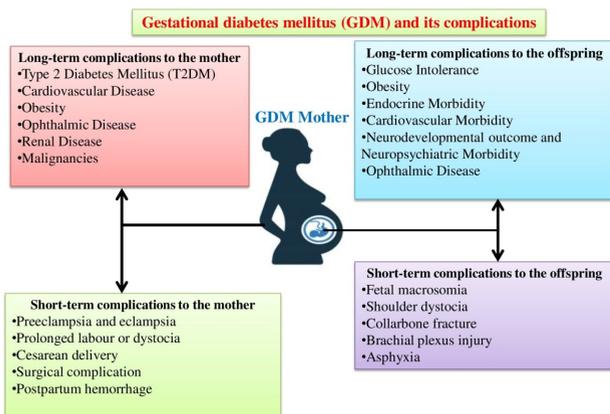


Fig. 2: The gestational diabetes mellitus and its complications

women with a history of GDM had a considerably greater prevalence of ophthalmic morbidity.³⁷ Up to 20% of women with GDM will develop T2DM years after giving birth, resulting in retinopathy.³⁸

3.5. Renal disease

GDM appears to be a major risk factor for long term renal morbidity. Hypertensive renal illness without renal failure, hypertensive renal disease with renal failure, chronic renal failure, and end-stage renal disease were the four most common future renal diagnoses.³⁹

3.6. Malignancies

Women having a history of GDM may be at a higher long term risk of malignancy development: hospitalizations for malignancies years after delivery were higher in women with GDM. The risk of ovarian, endometrial, and/or breast cancer has been linked to GDM.⁴⁰ Other research has found a link between GDM and higher glucose levels during pregnancy and an increased risk of breast cancer. Perrin et al. observed five instances of pancreatic cancer in women with GDM history over the course of a 28–40-year follow-up period, with an adjusted relative risk of 7.1.⁴¹ GDM women were also more likely to be diagnosed with pancreatic cancer, according to another study.⁴²

4. Short-term Complications to the Mother

4.1. Preeclampsia and eclampsia

Preeclampsia and eclampsia caused by pregnancy are still a big problem in developed countries. Increased knowledge and antenatal visits, along with good antenatal care, may assist to reduce the frequency of maternal and fetal problems. Increased illiteracy and poor socioeconomic level create a target group for medical interventions and public health programmes. Early detection of instances is aided by frequent blood pressure monitoring at every visit, a history of previous preeclampsia, and diabetes mellitus. Proper institutional management minimises maternal and fetal mortality due to preeclampsia and eclampsia.⁴³

4.2. Prolonged labour or dystocia

Prolonged labour is a complex disorder that has a detrimental impact on obstetric outcomes as well as women's experiences. Consensus is required in the classification and treatment of prolonged labour. Interventions must be carefully managed in order to maintain normal births and avoid abuse. Increased clinical skill and thorough documentation of labour progress in birth records are critical for identifying and classifying protracted labour and improving care for all women and their delivering experiences, regardless of whether they have experienced prolonged labour or not.²⁸

4.3. Cesarean delivery and surgical complication

The most common complication of a caesarean section is haemorrhage, which can occur during or after the procedure. However, there is no consensus on the true incidence; it is estimated that about 75% of obstetric haemorrhages occur following caesarean section. Obstetric haemorrhage and preeclampsia alternate first and second position as causes of maternal death in developing countries, with the World Health Organization adopting a rate of 10% worldwide in all births with a viable foetus.⁴⁴

5. Long-term Complications to the Offspring

5.1. Glucose intolerance

The offspring's development of T2DM is highly linked to the mother's diabetic intrauterine environment. In a multiethnic group, 30.4% with T2DM had been exposed to maternal diabetes, compared to 6.3 percent of nondiabetic children.⁴⁵ Over the course of a relatively short time, 31.1% of obese adolescents with normal glucose tolerance who were exposed to GDM developed impaired glucose tolerance/diabetes. The findings show that offspring of mothers who have had prenatal diabetes are at least 5 times more likely to acquire impaired glucose tolerance than those who have not had GDM.⁴⁶ Similarly, 21% of young with T2DM or prediabetes were offspring of women who had GDM treated with diet, compared to 4% of women in the general population.⁴⁷ Obesity and T2DM are extremely common among Pima people. T2DM is up to 6 times more common in Pima children who have diabetic or prediabetic mothers; T2DM occurs nearly exclusively in childhood and adolescence in the offspring of diabetic and prediabetic mothers.⁴⁸ There is evidence that the greater prevalence of diabetes and obesity in the offspring of diabetic Pima women is attributable to a combination of hereditary and environmental factors. Studies involving sibling pairs with one sibling born before and one after the beginning of mother diabetes have yielded interesting results: Offspring who were born after their mother got diabetes had a much greater risk of developing diabetes themselves.⁴⁹

5.2. Neuropsychiatric morbidity and neurodevelopmental outcome

Previous research reveals that offspring of diabetic mothers are at risk for poor neurodevelopment. Long-term neuropsychiatric morbidities in offspring exposed to GDM was studied in a population based study done in southern Israel. Autism spectrum disorder, eating disorders, cerebral palsy, obstructive sleep apnea, epilepsy, and infantile spasms were among the neuropsychiatric conditions investigated in this study.⁵⁰

5.3. Ophthalmic disease

A new study looked into whether children born to mothers who have GDM are more likely to have paediatric ocular morbidity. When compared to the other groups, the offspring of individuals with GDM treated with medication had a greater cumulative incidence of ocular morbidity. In a Cox multivariable model, GDM treated with medication was demonstrated to be an independent risk factor for long term ocular morbidity. The authors came to the conclusion that GDM treated with medicine was linked to a higher risk of long-term paediatric ocular morbidity.⁵¹

6. Short-term Complications to the Offspring

6.1. Fetal macrosomia

Macrosomia is a term that refers to an estimated foetal weight or birthweight of more than 4500 g, while a birthweight of more than 4000 g is also widely used to denote this disease. Macrosomia affects about 10% of all pregnancies, and the term is commonly used interchangeably with large for gestational age fetuses.⁵² A history of macrosomia, multiparity, maternal obesity prior to conception, excessive weight gain during pregnancy, advanced gestational age, and maternal diabetes as the biggest risk factor are all related with this syndrome; nevertheless, in many cases of high birth weight, the aetiology is unknown. Macrosomia has been linked to a higher risk of adverse birth outcomes, such as instrumental and/or caesarean deliveries, postpartum haemorrhage, shoulder dystocia, collarbone fracture, brachial plexus damage, and hypoxia, according to previous research.⁵³

7. Conclusion

GDM is becoming more common all over the world, mainly to an increase in maternal obesity. As was reviewed in this article, solid data exists regarding the GDM pathophysiology and its complications. Several studies found an association between short and long term complications of GDM for both mother and child. diagnosis of GDM and treating it effectively not only prevent adverse maternal and prenatal outcome but also future diabetes in both mother and child.

8. Source of Funding

None.

9. Conflict of Interest

The authors declare no conflict of interest.

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