Review Article

Gestational Diabetes Mellitus – The Modern Indian Perspective

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Abstract

Gestational diabetes mellitus (GDM) is a serious and most frequent health complication during pregnancy which is associated with a significant increase in the risk of maternal and neonatal outcomes. GDM is usually the result of β-cell dysfunction along with chronic insulin resistance during pregnancy. Seshiah *et al.* pioneer work led to the adoption of Diabetes in Pregnancy Study Group in India criteria as the norm to diagnose GDM, especially in the community setting. In 2014, the Maternal Health Division of the Ministry of Health and Family Welfare, Government of India, updated guidelines and stressed upon the proper use of guidelines such as using a glucometer for self-monitoring and the use of oral hypoglycaemic agents. The 2018 Government of India guidelines stress the importance of counselling about lifestyle modifications, weight control, exercise, and family planning.

Keywords: Gestational diabetes mellitus, historical perspective, lifestyle modifications, pathophysiology

Introduction

Diabetes mellitus is defined as a condition where there are high blood glucose levels caused by failure of insulin secretion or because of abnormalities of biological functions.[1] Diabetes is one of the most prevalent metabolic diseases in the world, and because morbidity and fatality are increasing in the human population, diabetes has become the third "silent killer" after cancer and cardiovascular disease.[2] The World Health Organisation Expert Committee on Diabetes in 1980 and the WHO Study Group on Diabetes Mellitus groups classified diabetes into two major forms, termed as insulin-dependent diabetes mellitus (IDDM, type 1 diabetes) and non-insulin-dependent diabetes mellitus [NIDDM, type 2 diabetes (T2D)].[3]

Type 1 diabetes mellitus (T1DM) is one of the most common paediatric endocrine illnesses. It is estimated that around 97,700 children with T1DM are living in developing nations, like India.[4] Every year, around 75,000 new children are diagnosed with T1DM.[5] Data collected from hospital-based studies in 1990 from India suggest that juvenile diabetics constitute about 1–4% of the total diabetic population with the increasing incidence of T1DM worldwide. T2D, which constitutes 90% of all cases of diabetes, earlier considered to be a disease of the affluent "Western" countries, has now spread globally and has become a major cause of disability and death affecting even younger age groups. Diabetes has become widespread in many developing economies, such as China and India.[6]

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy[7] and was first recognised in 1823.[8] The term "gestational diabetes" was coined by Carrington in 1957; however, it further received much attention after John O'Sullivan's publications during the years 1961–1964.[9]

GDM is a serious and the most frequent health complication during pregnancy, which is associated with a significant increase in the risk of maternal and neonatal outcomes. The complications include increased need for caesarean delivery, foetal macrosomia, risk of development of hypertension and T2D in the mother, and higher lifetime risk of obesity and T2D in the offspring.[10] The American

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Diabetes Association states that the incidence of GDM is between 1% and 14%, and it entraps approximately 7% of pregnancies.[11]

Historical perspective

- 1940s: It was recognised that abnormally high foetal and neonatal mortality was experienced in women who developed diabetes years after pregnancy.[12]
- 1950s: The term "gestational diabetes" was applied to what was thought to be a transient condition that affected foetal outcomes adversely, which then becomes less intense after delivery.[13]
- 1960s: O'Sullivan found that the degree of glucose intolerance during pregnancy was related to the risk of developing diabetes after pregnancy. He proposed criteria for the interpretation of oral glucose tolerance tests (OGTTs) during pregnancy that were statistically significant. GDM will be diagnosed if any of the two values has met or exceeded the threshold.
  1. Fasting: 90 mg/dl
  2. Whole blood glucose values after 100 g oral glucose intake 1 hr: 165 mg/dL
  3. 2 hr: 145 mg/dL
  4. 3 hr: 125 mg/dL.[14]
- 1980s: These cut-off points were adapted to Carpenter and Coustan criteria for measuring glucose and were applied to have a modern definition of gestational diabetes—glucose intolerance with onset or first recognition during pregnancy.[15] Although based on O'Sullivan's values for predicting diabetes after pregnancy, the diagnosis of GDM also identifies pregnancies at increased risk for perinatal morbidity.[16-18]
- Aetiology of GDM: Women more than 25 years old, with the history of GDM since the last pregnancy, history of T2DM, PCOS, obesity, and an increased maternal age and women of particular ethnic groups were found to be at high risk for GDM[19,20] [Figure 1].

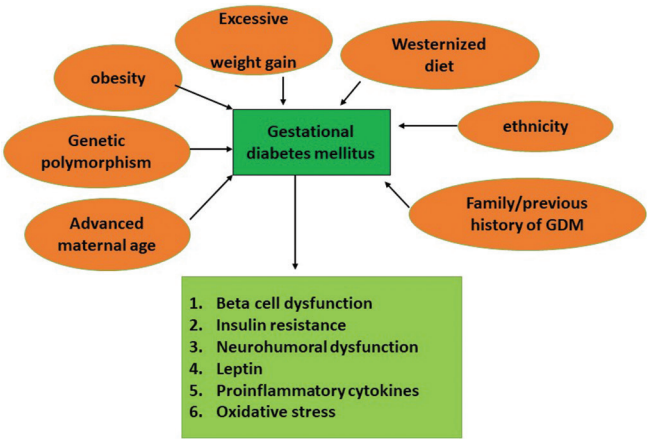


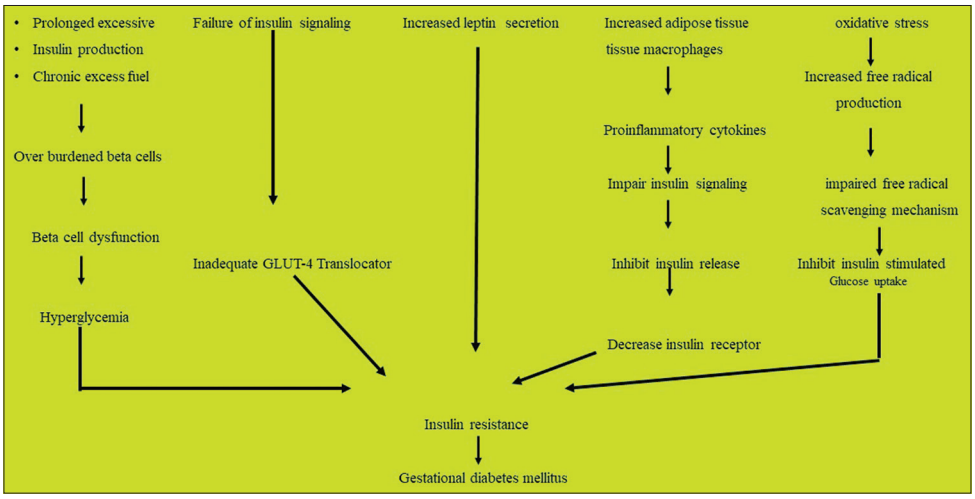
Figure 1: Aetiology of gestational diabetes mellitus

Pathogenesis

Pregnancy is a powerful psychological experience phase that impacts both pregnant women and their unborn children's long-term health.[21] The first trimester is an important phase as the foetus organogenesis occurs from week 3 through week 8.[22] During pregnancy, the developing foetus is completely reliant on the maternal environment for nourishment.[23]

- **Physiology of glucose regulation in normal healthy pregnancy**: During healthy pregnancy, the mother's body undergoes a series of physiological changes in order to support the demands of the growing foetus, with metabolic adaptations like insulin sensitivity and adaptations to the cardiovascular, renal, haematologic, respiratory, and metabolic systems.

  During early gestation, the mother's insulin sensitivity increases so that it promotes the uptake of glucose into adipose stores in preparation for the energy demands of later pregnancy.[24] As pregnancy progresses, there occurs a surge of local and placental hormones, including oestrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone, which together promote a state of insulin resistance [Flowchart 1].[25]



Flowchart 1: Pathophysiology

As a result, blood glucose is slightly elevated, and this glucose is readily transported across the placenta to fuel the growth of the foetus. This mild state of insulin resistance also promotes endogenous glucose production and the breakdown of fat stores, resulting in a further increase in blood glucose and free fatty acid (FFA) concentrations.[26] An animal study suggests that in order to maintain glucose homeostasis, pregnant women compensate for these changes through hypertrophy and hyperplasia of pancreatic β-cells as well as increased glucose-stimulated insulin secretion (GSIS).[27] The placental hormone, which is increased in this process, returns to pre-pregnancy levels within a few days of delivery.[28] For many reasons, the normal metabolic adaptations to pregnancy do not adequately occur in all pregnancies, resulting in GDM.

- **Pathophysiology of gestational diabetes mellitus:** GDM is usually the result of β-cell dysfunction on a background of chronic insulin resistance during pregnancy, and thus, both β-cell impairment and tissue insulin resistance represent critical components of the pathophysiology of GDM.

  The causes in cases where the normal metabolic adaptations to pregnancy do not occur are overweight/obesity,[29] excessive gestational weight gain,[30] westernised diet,[31] ethnicity,[32] genetic polymorphisms,[33] an advanced maternal age,[34] an intra-uterine environment, a low or high birthweight,[35] family and personal history of GDM,[36] and other diseases of insulin resistance, such as polycystic ovarian syndrome (PCOS).[37]

Genetic components of GDM

The studies in GDM have revealed that both genetic and epigenetic factors could play a role in GDM. The genetic factors are mostly related to single-nucleotide polymorphisms (SNPs) or gene mutations, whereas the epigenetic factors include gene methylation, histone modification, and microRNAs which can bind to mRNA.[38]

The SNPs rs7754840 and rs7756992 in the CDKAL1 gene were associated with GDM in South Indian women,[39] whereas variants in the HMG20A (rs7178572) and HNF4A (rs4812829) genes were associated with both GDM and T2D.[40] A study conducted in Rome showed an association between IRS-1 gene polymorphisms and GDM.[41] A meta-analysis found six polymorphisms of various genes which were associated with GDM. These genes included MTNR1B, TCF7L2, IRS-1, IGF2BP2, and TNF-alpha.[42] Other genes such as GCK, KCNJ11, and CDKAL1 also have been found to be associated with GDM.

Table 1: List of various studies on Gestational diabetes Mellitus in India

Place	Year of study	Sample size	Test done	Prevalence	Author
Rural Assam	July 2019- September 2019.	1212	Oral GTT	16.7%	Subrata Chanda *et al*.[47]
Kolkata	Aug 2016- July 2018	416	IADPSG	37.3%	Lipika Das Mukhopadhyay
			DIPSI	31.3%	*et al*.[48]
Lucknow, Uttar Pradesh	Aug 2016 -Sept 2017	162	8 h of overnight fasting and 75 g anhydrous glucose	22.64%	Arpit Gupta[49]
Telangana	January 2015-December 2016	32 428	elevated random blood glucose	5.4%	Goutham Swaminathan[50]
Kerala	January 2015 and December 2016	32 428	elevated random blood glucose	4.5%	Goutham Swaminathan[50]
West Bengal	January 2015 and December 2016	32 428	elevated random blood glucose	2.3%	Goutham Swaminathan[50]
Uttarkhand	January 2015 and December 2016	32 428	elevated random blood glucose	1.2%	Goutham Swaminathan[50]
Bihar (east),	January 2015 and December 2016	32 428	elevated random blood glucose	1.2%	Goutham Swaminathan[50]
Madhya Pradesh (central)	January 2015 and December 2016	32 428	elevated random blood glucose	1.2%	Goutham Swaminathan[50]
Uttar Pradesh (central)	January 2015 and December 2016	32 428	elevated random blood glucose	1.2%	Goutham Swaminathan[50]
Meghalaya Rajasthan Himachal Pradesh Manipur Assam Mizoram	January 2015 and December 2016	32 428	elevated random blood glucose	0.23%	Goutham Swaminathan[50]
Delhi	December 2015–October 2016	100	75 g oral glucose test	14%	Samreen Siddiqu[51]
Bhilai	(December 2015–October 2016	65	1 hour 75 gm glucose	10.7%	Samreen Siddiqu[51]
Muzaffarpur	(December 2015–October 2016	65	Fasting blood glucose	3.07%	Samreen Siddiqu[51]
Pune, Maharashtra	September 2012 to June 2014	989	2 h post 75 g glucose	9.5%	Anjali A. Bhatt[52]
Lucknow	June 2012 to July 2013	332	2 hrs 75 g OGTT	41.9%	V Gopalakrishna[53]
Punjab	August 2009-December 2012.	5100	WHO 2013 criteria	35%	Geeti P Arora *et al*.[54]
			WHO 1999 criteria	9%	
Kashmir	April 2011 - March 2012.	306	75 g OGTT	7.8%	Malik Waseem Raja *et al*.[55]
Rohtak	June 2009 to January 2011	607	75 g 2 h OGTT	7.1%	Rajesh Rajput[56]
Chennai	February- December 2001	1251	2 h 75 g glucose ≥140	17.7%	V Seshiah *et al*.[57]
Bangalore	1991	302	3 hrs OGTT	6.3%	Jaya Narendra *et al*.[58]

A case control study from India found that microRNA7 was elevated in placental tissue as well as maternal and cord blood in GDM patients. The expression of IRS1, IRS2, and RAF1 was also lower in maternal blood, presumably as a consequence of elevated miRNA7.[43] The mutation or insertion deletion of mitochondrial tRNA genes was also associated with GDM in one study from India.[44] Variants of hexokinase domain containing 1 (HKDC1) gene were also found to be associated with GDM. The association of this gene with GDM was reported for the first time in this study.[45]

Gestational diabetes: trend in India

India is recognised as the world's diabetic capital, and also GDM is a serious concern in India compared to the other parts of the world, affecting particularly pregnant and lactating women.[46] The 1997 WHO estimates of the prevalence of gestational diabetes in adults showed an expected total rise of >120% from 135 million in 1995 to 300 million in 2025. Table 1 provides information on various studies of GDM conducted in india.

Global prevalence of gestational diabetes mellitus

The International Diabetes Federation (IDF) reported that the global prevalence of GDM ranges from 1% to 14% in 2014.[59] In 2017, the global prevalence of GDM adversely affected 16.2% of all live births, with GDM accounting for 86.4%.[60] In Europe, the prevalence of GDM varied significantly, and in some populations, more than 20% of pregnancies have been documented.[61] Prevalence rates for GDM climbed to 14% of the pregnancies among U.S. women.[62]

Diagnosis: Seshiah *et al.* pioneer work led to the adoption of Diabetes in Pregnancy Study Group in India (DIPSI) criteria as the norm to diagnose GDM, especially in the community setting. The DIPSI criteria are one of the criteria recommended by the Government of India to diagnose GDM. DIPSI recommends a non-fasting OGTT based on the belief that fasting OGTT would be very difficult for pregnant women in the community as it requires travel to the clinic on a separate day.[63] The blood glucose level of ≥140 mg/dl 2 hours after the consumption of 75 mg of anhydrous glucose was considered GDM. DIPSI criteria are well-known criteria for the detection of GDM. The need for a simple screening test for GDM is undoubtedly important, considering its relevance for the large population. The evidence base of the DIPSI criteria is a singlecentre study comparing non-fasting OGTT with WHO 1999 criteria, showing 100% sensitivity and specificity.[57]

Complications

Maternal: A recent meta-analysis showed that women with gestational diabetes have a greatly increased risk of developing T2D (relative risk 7.43, 95% confidence interval 4.79–11.51). GDM also influences immediate maternal outcomes like pre-eclampsia, stillbirths, and need for caesarean section.[64]

Foetal: The glucose levels of pregnant women play a crucial role in GDM. If they are not adequately regulated, they can cause foetal hyperinsulinemia, neonatal hyperglycaemia, and excess foetal growth, known as macrosomia.[65,66] Moreover, hyperglycaemia during pregnancy could produce[67,68] foetal birth trauma, neonatal hypoglycaemia, large for gestational age, delayed lung growth, and foetal hypoxia.[67,69]

Management

In 2014, the Maternal Health Division of the Ministry of Health and Family Welfare, Government of India (MOHFW) published the national guidelines for the diagnosis and management of GDM in India.[70] They recommended the DIPSI test at first visit, and if it is negative, they recommended to repeat it between 24 and 28 weeks gestation for all pregnant women. MOHFW guidelines were updated using national and international studies in 2018.[71] As in the first recommendations, testing a woman two times remained central to the updated guidelines.[72] Updated guidelines stressed the proper use of operational guidelines using the glucometer for self-monitoring (SMBG) and the use of oral hypoglycaemic agents (OHAs). The use of oral hypoglycaemic metformin has been approved for use in GDM after 20 weeks of gestation by the Central Drugs Standard Control Organization of India, which is the pharmaceutical watchdog, equivalent to the US Food and Drug Administration (FDA). The advantages of oral hypoglycaemics are as follows: They are easy to take being an oral medication, more readily acceptable to the patient (compared to insulin), and much cheaper. They also limit the use of insulin to a selected few women—those who cannot tolerate metformin or women in whom metformin fails to control the plasma glucose.

Lifestyle modifications

Women with GDM after delivery can be helped to prevent the epidemic of T2DM through preventive strategies,[64] but most women with GDM are lost in follow-up after delivery. A study conducted in India on women with GDM after delivery[73] with strict post-partum follow-up for 17 months was completed with six sessions on lifestyle modifications. All indices of metabolic health improved (weight, glycaemia, lipids, and BP), and 70% of women with prediabetes post-partum reverted to normoglycaemia. The 2018 Government of India guidelines stress the importance of counselling about lifestyle modifications, weight control, exercise, and family planning. The post-partum follow-up of women with GDM with strict preventive and lifestyle modifications remains important in order to turn the tide of the epidemic of T2DM.

Discussion

The worldwide prevalence of GDM is rising in parallel with the rise in the prevalence of overweight and obesity among pregnant women, and it is linked to physical inactivity, food habits, advanced maternal age, and ethnicity.[74] Obese pregnant women may be at a higher risk of homeostatic dysregulation during pregnancy due to metabolic changes that occur during pregnancy, including decreasing insulin sensitivity in late pregnancy. In the study, insulin resistance is approximately 40% higher in obese women than in normal-weight women.

Hence, maternal age and early pregnancy BMI are more important risk factors for GDM.[60] Early gestational weight gain also has significant association in the development of GDM.[75] Pre-eclampsia, large-for-gestational-age infants, and pre-term birth are all connected with excessive gestational weight gain, which also increases the risk of post-partum weight retention.[76] Recently, there has been increasing attention to the role of maternal mental health in developing GDM. It is widely established that maternal food patterns during late pregnancy can put infants at risk of obesity later in life. Moreover, the risk of obesity is elevated in the offspring of women with GDM.[77] Dietary fat consumption in particular has been linked to increased GDM risk. Apart from a fat-rich diet, milk products were the only food group that has been recognised as significantly related to an increase in GDM. Here, it illuminates that the most powerful modulator of GDM risk before conception is presumably normalising body weight.[75]

Conclusion

There might be exotic influence on Indian dietary patterns along with eccentric changes in our living style and lifestyle adoptions. As incidence and prevalence of GDM are increasing in India, it is necessary for early detection and intervening with suitable treatment. The women with GDM should be educated regarding diet, lifestyle modification, and complications after delivery. A detailed study on genetic components and also biomarkers plays a very important role in early detection of GDM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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