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A NARRATIVE REVIEW OF PATHOGENESIS OF GESTATIONAL DIABETES MELLITUS.

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ABSTRACT.

Gestational Diabetes Mellitus (GDM) is characterized by impaired glucose metabolism that initially becomes evident during gestation. This narrative review provides a comprehensive overview of various aspects of the pathogenesis of GDM, shedding light on its risk factors, genetic factors, and implications for postpartum health. Extensive epidemiological research has revealed a correlation between increasing environmental temperatures and a heightened risk of GDM, often associated with diminished β-cell function. Key elements contributing to the development of GDM include β-cell dysfunction and insulin resistance in bodily tissues. Genetic investigations have pinpointed common genetic variations as culprits for both GDM and T2DM. Women who experience GDM face an elevated possibility of emerging T2DM in later periods of life. Additionally, those with a past of GDM are 7 times more prone to postpartum diabetes than individuals without such a history. Various factors, such as maternal age, pregnancy-related glucose conc., family medical history, pre-gestation and postpartum BMI, dietary habits, bodily movement, and breastfeeding, have been identified as risk variables for postpartum diabetes among females with GDM. Furthermore, females with GDM have an amplified susceptibility to conditions like pre-eclampsia or eclampsia during pregnancy, rendering them more at risk for cardiovascular diseases. Consequently, the management of GDM is primarily aimed at mitigating difficulties for both the mother and the fetus, maintaining optimal glycemic levels, and preventing excessive weight gain. Future research should focus on further understanding the pathogenesis of GDM, identifying modifiable risk factors, and developing effective interventions. In clinical practice, managing GDM involves maintaining optimal glycemic levels, preventing excessive weight gain, and implementing lifestyle changes such as therapeutic measures, exercise, dietary modifications, and low-glycemic-index diets to mitigate post-meal hyperglycemia and reduce insulin resistance. Addressing GDM effectively is crucial for the well-being of both mothers and their babies.

Keywords: Gestational Diabetes Mellitus (Gdm), Pathogenesis, Risk Factors, Genetic Factors, Postpartum Health, Insulin Resistance.
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INTRODUCTION.

Gestational diabetes mellitus (GDM) is a frequently encountered complication identified by the occurrence of impulsive hyperglycemia throughout pregnancy. It is estimated that GDM affects approx. 16.7 percent of pregnant females globally.[1] The etiology of this condition can be attributed to the secretion of a hormone synthesized by the placenta, which hinders the body's efficient utilization of insulin. Consequently, there is a build up of glucose within the bloodstream, as opposed to its uptake by the cellular structures. [2] GDM identified during the later stages of pregnancy has a more pronounced impact on placental function. The placentas of people with GDM commonly display characteristic histological features, including villous fibrinoid necrosis, villous immaturity, heightened angiogenesis, and chorangiosis. These pathological changes ultimately impact the transfer of nutrients to the developing fetus, resulting in disruptions to fetal growth and development.[3,4] Women diagnosed with GDM may also be susceptible to the development of pre-eclampsia, spontaneous pregnancy termination, preterm labor, and the need for a caesarean section.[3,4] Moreover, gestational diabetes mellitus (GDM) escalates the susceptibility to various complications in the offspring, including birth trauma, hypoglycemia, and respiratory distress. Simultaneously, it heightens the likelihood of type 2 diabetes mellitus (T2DM), coronary artery disease, and obesity in the mother.[3,4]

The key question identified for the review topic could be: "What are the etiology, clinical implications, and maternal-fetal outcomes associated with gestational diabetes mellitus (GDM)?"

METHODOLOGY.

Using PubMed search criteria that included " Gestational Diabetes Mellitus Pathogenesis," this narrative review makes use of the scant primary data currently available from a literature search. Additional data was obtained from Internet searches of credible and well-known organizations, such as the World Diabetes Foundation, the World Health Organization (WHO), the International Association of the Diabetes and Pregnancy Study Groups (IADPSG),

governmental organizations, and other institutions as cited. The utilization of the narrative technique has enabled a thorough evaluation of the obstacles and deficiencies impeding the advancement of diabetes treatment in pregnant women, while also pinpointing possible avenues for growth.

Epidemiology.

Certain groups of Asian women exhibit a higher propensity for GDM in comparison to Caucasian women, particularly, Indian women with an 11-fold increased likelihood of developing glucose intolerance during pregnancy.[5] Based on the criteria formulated by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG)/World Health Organization (WHO) 2013, there is a high prevalence of GDM in European pregnant women with a body mass index (BMI) of 29.0 kg/m2 and it poses a significant health burden to these pregnancies along with the health of the mother and the neonate in later life.[6]

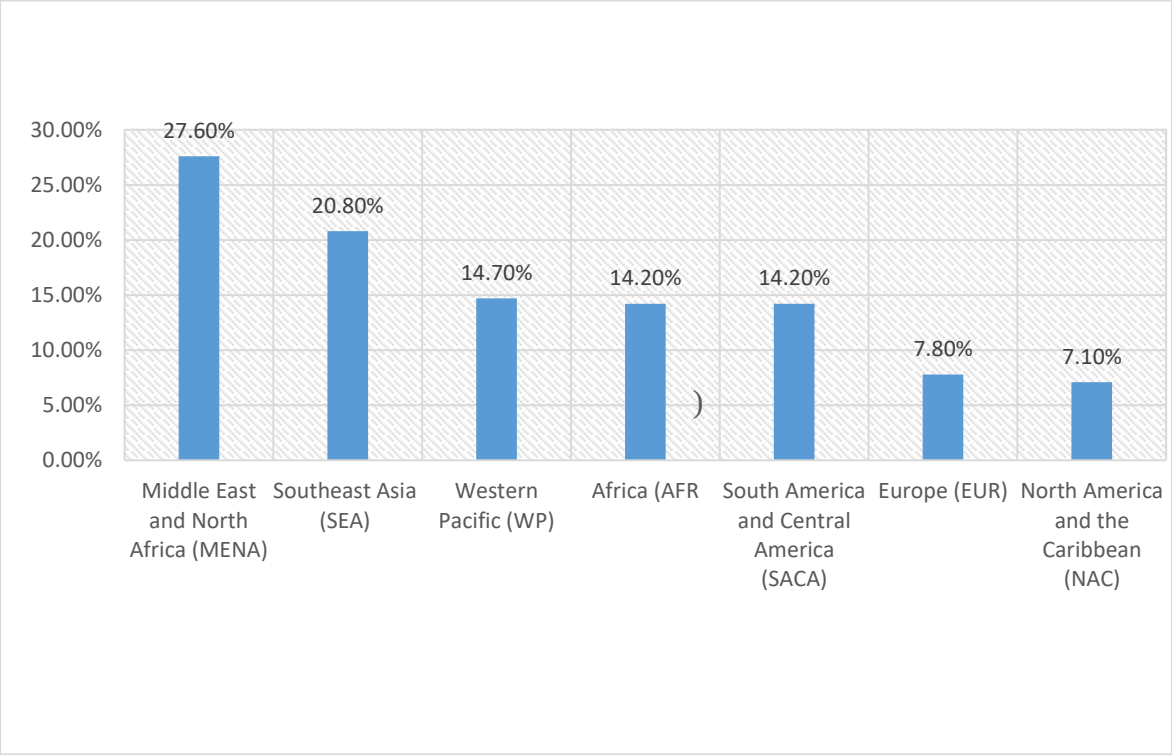

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Figure 1. The geographical distribution of GDM.[7]

In 2013-14, over six million pregnant women in India experienced hyperglycaemia, of which 90% had GDM. Research on the occurrence of GDM across India are briefed in Figure 2.

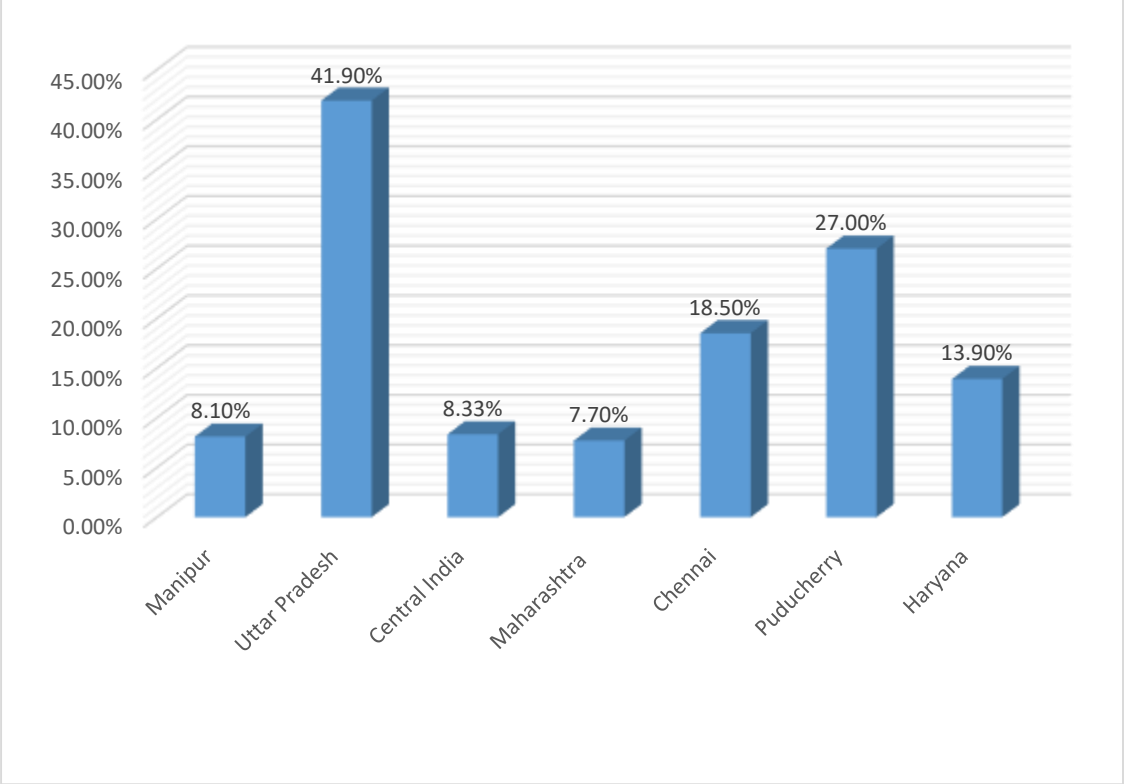
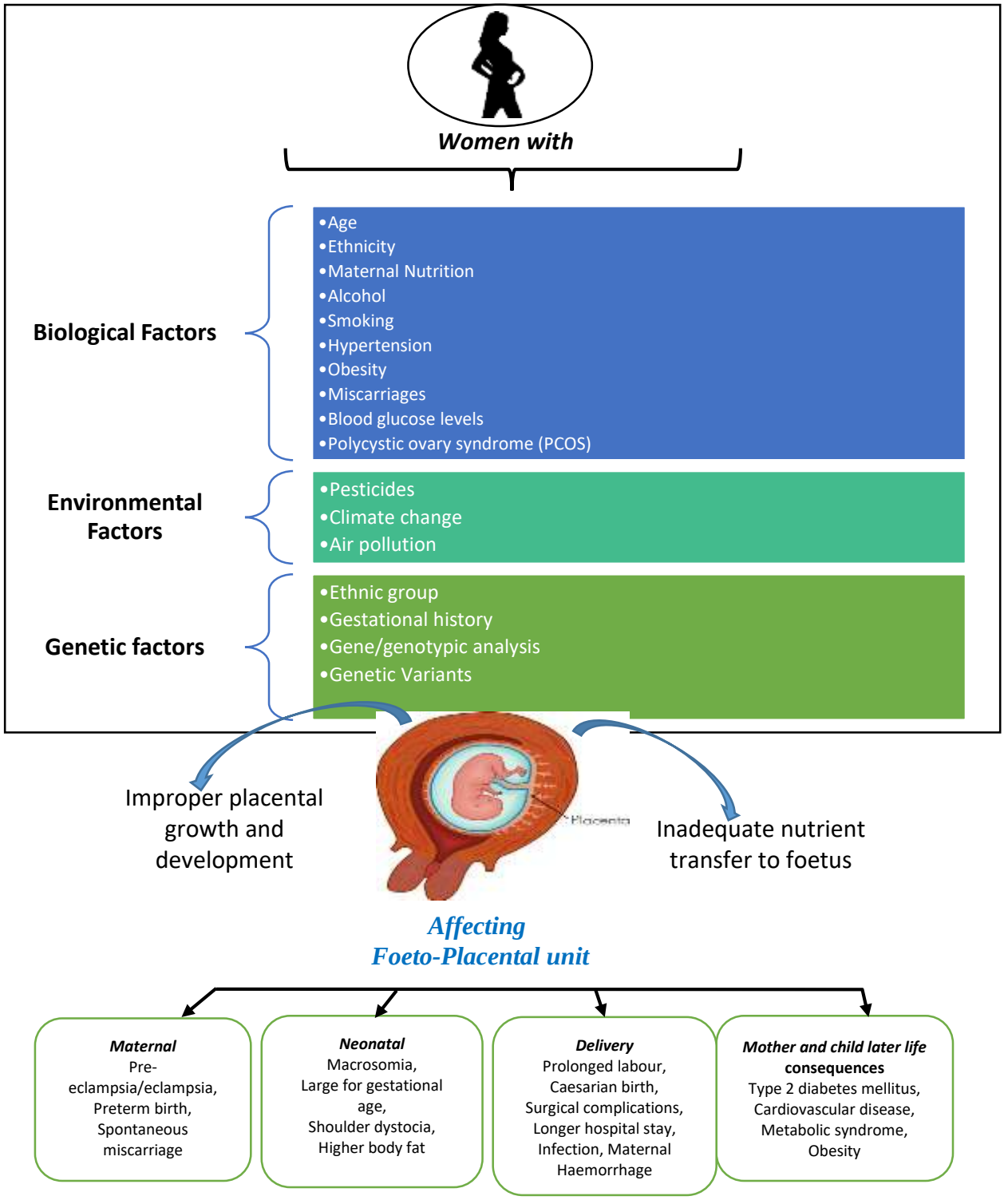


Figure 2. Prevalence of GDM in India.[8]

Risk factors for GDM

The risk variables for GDM including biological, environmental, and genetic components, increase the likelihood of maternal metabolic syndromes and pregnancy complications that ultimately affect foetal growth and development (Figure 3).

Figure 3. Maternal risk factors associated with GDM



Biological factors.

A comprehensive study of 24 research works has demonstrated a strong relation between maternal age and GDM (*P*trend < 0.001) for the overall population; the risk for GDM rose by 7.90%, 12.74%, and 6.52% in the total number of subjects, Asian, and Europid participants respectively9. Another study also reported that the frequency of GDM demonstrated a statistically significant positive correlation with advancing maternal age, with an average increase of 8% per year.[10] Advanced maternal age and non-Australian birth elevate the susceptibility to GDM, primarily among Asian women.[11]

In a work conducted by Yaping *et al*., it was detected that individuals with a history of 3 or more miscarriages exhibited a 6.382-fold higher probability of developing gestational diabetes mellitus (GDM) (Odds ratio [OR] = 6.382, P <0.05). These findings suggest a positive association between the number of miscarriages experienced and an elevated susceptibility to GDM.[12] A positive association of GDM and advanced maternal age, pre-pregnancy BMI, extreme weight increase during pregnancy, cessation of cigarette smoking, family past of diabetes, and previous past of GDM.13 Within this cohort, it was observed that elevated pre-pregnancy BMI and excessive pregnancy mass gain exhibited a statistically significant correlation with increased susceptibility to adverse outcomes stemming from GDM.[14, 15]

In a meta-analysis conducted by Qiu *et al.*, it was detected that females diagnosed with PCOS exhibit a significantly elevated susceptibility to GDM when related to females not having PCOS (P <0.0001).[16] The ingestion of a Western diet in conjunction with an elevated consumption of overall fat and saturated fatty acid before or during the initial stage of gestation is correlated with a potential augmentation in the susceptibility to the onset of GDM.17 In contrast, a dietary pattern characterized by vegetarianism demonstrated an association with a decreased risk of GDM. Conversely, consumption of sweets and seafood exhibited contrasting outcomes, with an elevated risk of GDM observed.[18]

Environmental factors.

Women exposed to medium and high concentrations of polychlorinated biphenyls (PCBs) had higher odds (3.90 and 3.60-fold, respectively) of developing GDM.19 A multicenter prospective cohort study was conducted to examine the relation among elevated conc. of polychlorinated biphenyls (PCBs) containing 6 or more chlorine atoms and the risk of GDM in a cohort of American females. The research findings revealed a positive correlation between a higher number of PCBs with more than 6 Cl atoms and an elevated risk of GDM within the entire cohort. The risk ratios observed in the study ranged from 1.08 to 1.13 per 1- SD increase. However, in females with a family past of T2 DM, the risk ratios [RRs] ranged from 1.08 to 1.48 per 1-SD increment.[20]

Epidemiological research has shown a through correlation between elevated ambient temperatures and the susceptibility to both gestational diabetes mellitus (GDM) and impaired β-cell function.[21] A systemic data analysis by Preston *et al*., revealed a seasonal effect with a higher occurrence of GDM and elevated glucose levels during the summer. Increased ambient temperature is also related to high glucose levels, as observed during analysis for GDM.22 Moreover, data from a meta-analysis indicated that ambient air pollution (nitric oxide, nitric dioxide, ozone, and sulphur dioxide) was associated with the growth of GDM.23 A retrospective unit study also stated that contact with particulate matter in the 2nd trimester of gestation was related to an elevated risk of GDM.[24]

In a research conducted by Booth *et al.*, it was observed that the prevalence of GDM was 4.6% among women who had been subjected to seriously cold mean outside temperature (≤10 °Celcius) in the 30 days before analysis. This prevalence elevated to 7.7 percent between females who had been subjected to hot average temperatures (≥24 °C) during the same time frame. Furthermore, it was observed that for every increase of 10° Celcius in the mean 30-day temp., there was a corresponding 1.06 folds higher likelihood of developing GDM.[25]

Genetic Factors.

Epigenetic changes characterized by alterations in gene expression by factors other than genetic variants include gene methylation, histone modification, and binding of microRNAs (miRNAs) to mRNA.26 The genetic variants including the rs1800796 G allele [interleukin-6], rs1800896 C allele [interleukin-10], and the rs1800629 A allele [TNF-α], were suggestively related to an elevated risk of exposure to GDM.27 Another study reported the positive association between rs7903146 [TCFL2], rs13266634 [*SLC30A8*], rs2283228 [*KCNQ1*], rs5210 [*KCNJ11*], and rs1799831 [*GCK*] with GDM].[28]

A new study by Bhushan *et al*. reported that elevated levels of miRNA-7 may be related to the development of GDM. MiRNA-7 alters many pathways like insulin, gonadotrophin-releasing hormone (GnRH), and inflammatory signaling, thus associating a new treatment target for GDM.29 Genetic variants including rs7178572 [High Mobility Group 20A (HMG20A)] and rs4812829 [HNF4A] were related with GDM in the Asian Indian population.[30]

Pathogenesis of GDM.

Insulin sensitivity and resistance in pregnancy.

As the gestational period advances into the 3rd trimester, it is observed that the sensitivity of insulin may exhibit a gradual decline, reaching approximately 50% of the anticipated normative value, which is mediated by a variety

of mechanisms including an increase in oestrogen, progesterone, and human placental lactogen (hPL), among others.31 Both β-cell dysfunction and resistance to insulin contribute to the persistent hyperglycemia that is a characteristic of T2DM. A recent study conducted on pregnant women in the 2nd trimester has documented elevated levels of resistance to insulin and β-cell dysfunction, which subsequently heightens the susceptibility to GDM.32 The findings of clinical studies have revealed a significant correlation between dysfunctional β-cells and females detected with GDM in comparison to the non-GDM cohort (P <0.05).33 The observed outcomes may be attributed to the inability of β-cells to adequately respond to the heightened demand for insulin secretion during the latter stage of pregnancy, characterized by the peak of insulin resistance.

Hormonal effect in normal and diabetic pregnancy.

Reproductive hormones tend to rise during pregnancy, most of which contribute to insulin resistance and altered β-cell function.

Oestrogen and progesterone.

During the initial phases of pregnancy, there is an elevation in the concentrations of oestrogen and progesterone, both of which exhibit a direct correlation with insulin resistance.[34] In GDM cases, the levels of both oestrogen and progesterone were lesser in GDM cases.[35] The expression of genes encoding oestrogen receptors α and β was suggestively decreased in the subcutaneous adipose tissue of females with GDM as compared to the control group signifying a possible part in the regulation of resistance of insulin.[36]

Cortisol.

Cortisol has a vital role in the pathophysiology of hyperglycemia in GDM. This could be ascribed to pregnancy which is a long-standing stressor for women, contributing to higher cortisol levels. While elevated cortisol during pregnancy promotes insulin antagonism, lower serum cortisol levels in GDM are associated with fasting insulin levels and positively correlated with fetal development. Additionally, heightened concentrations of cortisol were observed during the phase of impaired glucose metabolism in expectant females, thereby resulting in diminished insulin sensitivity in gestational diabetes mellitus.[37]

Prolactin.

A systematic review of available data indicates a noteworthy correlation between elevated amounts of prolactin in mothers and decreased insulin levels, impaired β-cell function, and heightened insulin sensitivity during the post-partum period.[38] Elevated levels of prolactin during the 3rd trimester of pregnancy have been observed to be linked with compromised glucose tolerance. This association suggests that prolactin may possess an autonomous function in the growth of GDM.[39]

Leptin.

Females diagnosed with GDM exhibited a significantly elevated baseline conc. of leptin (P <0.0001) in correlation with their GDM status.[40, 41] Elevated concentrations of leptin have been observed in the prevailing pathological condition of GDM. In this context, it is postulated that leptin may serve as a mediator for the heightened growth of the placenta and the growing fetus, thereby potentially playing a role in the occurrence of macrosomia[42]

Other Factors.
TNF-α

Tumor necrosis factor-alpha (TNF-α) facilitates the process of serine phosphorylation of the insulin receptor substrate-1 (IRS-1) by acting upon the insulin receptor. There have been reports indicating a notable correlation between elevated conc. of TNF-α and heightened insulin resistance among females diagnosed with gestational diabetes mellitus. Furthermore, it has been suggested that TNF-α may impede insulin signaling pathways.[43]

Adrenomedullin.

Elevated levels of circulating adrenomedullin (ADM) were observed in pregnant females detected with GDM, potentially playing a role in the impaired adaptation of β-cells in pregnant females with diabetes. It is suggested that inhibiting the interaction between ADM and its antagonists could potentially enhance β-cell function.[44] A separate investigation revealed that pregnant individuals exhibiting increased levels of serum ADM conc. (P = 0.008) experienced a significantly heightened susceptibility to the development of GDM.[45]

Adiponectin.

A study was conducted to examine the adiponectin levels in people with GDM as compared to control subjects. The analysis revealed a statistically relevant variance in the mean adiponectin level among the two groups. Specifically, the GDM patients exhibited a significantly lower mean adiponectin level compared to the control subjects (SD = −1.514, 95% confidence interval = −2.400 to −0.628, p-value = 0.001, I2= 99%). The risk of GDM exhibited a notable decrease in pregnant females as the amount of circulating adiponectin increased (odds ratio [OR] = 0.368, 95% confidence interval [CI] = 0.271–0.500, p-value < 0.001, I-squared [I2] = 83%).[46] Moreover, a preliminary investigation conducted on individuals of Asian Indian descent has demonstrated that the levels of adiponectin in

the bloodstream during the initial trimester of pregnancy could potentially serve as a robust indicator for gestational diabetes mellitus (GDM).[47]

Gut microbiome.

A potential diagnostic modality that could contribute to the prevention and administration of GDM is the examination of the gut microbiome in pregnant patients during the 2nd trimester.[48] The most commonly noted alteration in the microbiome of individuals diagnosed with GDM was either an augmentation in the *Firmicutes* phylum or a reduction in the *Actinobacteria* and *Bacteroidetes* phyla.[49]

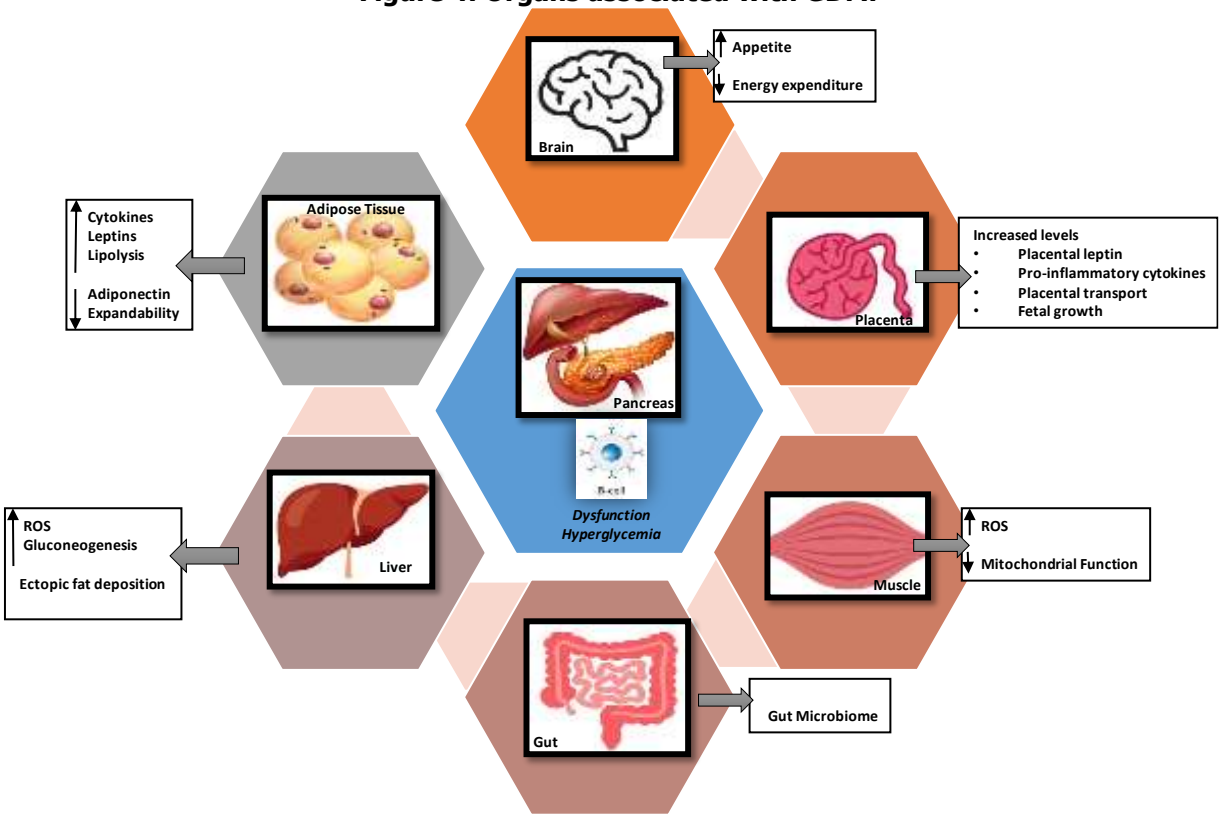
Oxidative stress.

GDM is related to elevated oxidative stress due to both free radical overproduction and a deficiency in anti-oxidant mechanisms. This increase has severe consequences on the mother's health, placental function, and fetal health.[50]

Organs involved in the pathophysiology of GDM.

GDM commonly arises due to impaired β-cell function, leading to persistent insulin resistance throughout pregnancy. GDM exerts its influence on a diverse array of bodily organs, encompassing the brain, adipose tissue, hepatic system, musculature, and placental structure (See Figure 4).[2]

Figure 4. Organs associated with GDM.[2]



The coexistence of obesity and GDM is characterized by a correlation with an augmented populace of the resident macrophages within the adipose tissue. The secretion of pro-inflammatory cytokines including TNFs and IL-6 and IL-1, by these macrophages suggests a potential involvement of chronic low-grade inflammation in the growth of GDM. Adipose tissue plays a vital role in the efficient breakdown of energy and also serves as an active source of various circulatory factors, including adipokines (such as adiponectin and leptin) and cytokines such as TNF, IL-6, and IL-1, which exert significant metabolic influences. Thus, the adipose tissue storage capacity is critical for metabolic health.[2] GDM is related to increased hepatic glucose synthesis, also known as gluconeogenesis. Fasting causes an increase in gluconeogenesis, which is not properly inhibited in the "fed" state. The common components between insulin signaling and the gluconeogenic pathways, such as phosphatidylinositol 3-kinase (PI3K), may contribute to these effects. Elevated protein consumption and muscle collapse may further speed up the process by supplying more substrate for gluconeogenesis.[51]

T2DM was assumed to be caused by insulin resistance of skeletal muscles; conversely, this resistance of insulin seems to be a result of hyperglycemia - a defensive strategy to avert metabolic stress and steatosis. T2DM and GDM, in addition to insulin sensitivity, are associated with a decrease in the quantity and activity of mitochondria inside the skeletal muscle cells. This could be due to genetic factors, early childhood programming, or chronic inactivity. As a result, a decrease in the no. and function of mitochondria are probable contributing factors to the impaired glucose utilization in GDM.[2,52]

The placenta assumes a vital role in the advance of resistance to insulin during gestation, primarily by its ability to synthesize and release various hormones and cytokines. Hence, the placenta serves as a protective interface separating the maternal and fetal environments, rendering it susceptible to the adversative effects of hyperglycemia in the context of GDM. This has the potential to exert an influence on the placental transfer of carbohydrates, amino acids, and lipids. Furthermore, GDM has been related to a multitude of aberrations in the placental structure and function.[2]

Recent investigations have revealed a link between GDM and global placental DNA hypermethylation.[53] Furthermore, recent research indicates that the gut microflora, the collection of microbes inhabiting the digestive system, may play a role in the development of metabolic conditions like Gestational Diabetes Mellitus (GDM). This complex microflora can be impacted by various life events, including early factors such as preterm birth and breastfeeding, as well as later factors like dietary choices and antibiotic usage. Certain bacterial families, such as *Prevotellaceae*, can break down mucin, potentially resulting in higher intestinal permeability. The control of gut permeability is overseen by tight junction proteins, including zonulin (ZO-1). Elevated levels of free ZO-1 in plasma or serum have been linked to Gestational Diabetes Mellitus (GDM).54 Neurohormonal dysfunction plays a role in the advance of insulin resistance disorders like GDM. It influences various aspects of metabolism, including active energy expenditure, basal metabolic rate, and appetite. This intricate regulatory system involves both central components, such as cortical centers responsible for visual, reward-related cues, and peripheral elements like satiety, cognitive, and starvation hormones.[2]

The association between insulin resistance in normal pregnancy and GDM

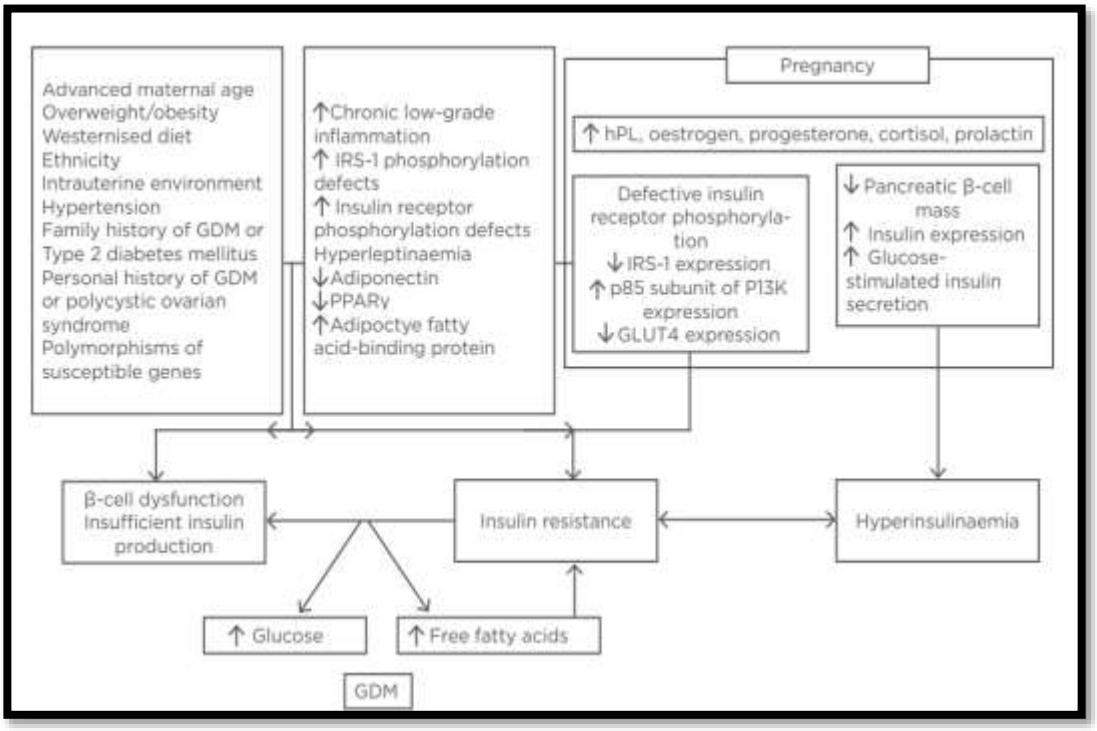


Figure 5. Insulin resistance in normal pregnancy and GDM pathway (Adapted from [55])

During gestation, there is a notable physiological reduction in peripheral insulin sensitivity. This decline is influenced by various factors, such as elevated concentrations of oestrogen, hPL, progesterone, prolactin, and cortisol among other variables. The peripheral insulin signaling cascade components are modulated, concomitantly with the activation of multiple pathways that enhance β-cell function. GDM arises as a consequence of inadequate insulin production, which proves insufficient to respond to the physiological insulin resistance that occurs during gestation.

During and after delivery, there is an observed modification in the expression of downstream effectors involved in the insulin signaling pathway. Notably, there is a noticeable alteration in the expression levels of insulin receptor substrate (IRS)-1, phosphoinositide 3-kinase (PI3K), and glucose transporter 4 (GLUT4). Additionally, there is a decrease in the expression of peroxisome proliferator-activated receptor, while there is an increase in the expression of the membrane glycoprotein PC-1 (see Figure 5).[55]

Long-term consequences for mother and child in GDM.

There is substantial evidence between GDM and long-standing maternal coronary artery disease with a prevalence of approximately 9%.
Further, GDM was linked to additional long-term maternal problems such as kidney, ocular, and even cancerous diseases. Moreover, studies have found a relation between GDM and lasting complications in the progeny.[56] While the risk for most illnesses is generally modest, there is a considerable risk (approximately 8%) for child endocrine morbidity.[57] There are several pharmacological therapies for GDM, including insulin and oral glucose-lowering medications, metformin, and glibenclamide. Although the short-term paediatric outcomes of these oral drugs appear comparable to insulin, an increasing body of evidence suggests potential lasting adverse effects on both the offspring and adults who have been exposed to these therapeutic interventions during the prenatal period.[58]
Lastly, valid assessments of dietary patterns and diet quality are mandatory to govern the maternal dietary consumption and risk of GDM. The dietary pattern and quality vary depending on the geographical region, culture, and economy per capital of a country, as well as the population.[59]

LIST OF ABBREVIATIONS:

GDM: Gestational Diabetes Mellitus
T2 DM: Type 2 Diabetes Mellitus
BMI: Body Mass Index
WHO: World Health Organization
IADPSG: International Association of The Diabetes and Pregnancy Study Groups
OR: Odd Ratio
PCOS: Polycystic Ovary Syndrome
PCBs: Polychlorinated Biphenyls
RRs: Risk Ratios
GnRH: Gonadotrophin-Releasing Hormone
hPL: Human Placental Lactogen
TNF-α: Tumor Necrosis Factor-Alpha
IRS-1: Insulin Receptor Substrate-1
ADM: Adrenomedullin
PI3K: Phosphatidylinositol 3-Kinase
ZO-1: Zonulin
GLUT4: Glucose Transporter 4

CONCLUSION.

The management of GDM holds paramount importance due to the elevated risk of T2DM in females with GDM within 5-10 years following pregnancy. Moreover, the children born from pregnancies affected by GDM exhibit increased susceptibility to obesity and T2DM. Insulin resistance is triggered by a mixture of upsurged maternal obesity and the insulin-desensitizing effects of placental hormone secretions. These placental hormones play a pivotal role in inducing this condition of resistance. Pancreatic β-cells generally upsurge insulin synthesis to compensate for pregnancy-induced insulin resistance. Normal glucose management throughout pregnancy is distinguished by the remarkable plasticity of β-cell function in the face of growing resistance to insulin.
The Developmental Origins of Health and Diseases (DOHaD) theory conceptualizes the significant impact of nutrient intake and maternal nourishment on pregnancy results and the subsequent lasting risk of chronic diseases. This influence is believed to occur through a transgenerational flow. GDM management is complicated in India and has multifaceted issues. However, there is a scarcity of data highlighting these problems. Through this review, we have discussed some of the significant issues from the perspective of self-management and healthcare.

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We would like to acknowledge the valuable contributions of healthcare professionals, researchers, and organizations working tirelessly to address the challenges posed by diabetes in India. Their dedication and efforts are instrumental in improving healthcare outcomes and reducing the burden of preventable diseases.

DOHaD: Developmental Origins of Health and Diseases

CONFLICT OF INTEREST.

The authors report no conflicts of interest in this work.

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