Review Article

A Critical Review on Varied Aspects of Gestational Diabetes Mellitus (GDM) and It's Associations with Placenta

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Abstract

Gestational diabetes mellitus (GDM) is defined as first onset hyperglycemic state during pregnancy. It is a common complication of pregnancy, caused by a combination of genetic and environmental factors. The pathophysiology of GDM is not yet fully understood. Placenta is an organ developed in gestational period and acts as a bridge between fetal and maternal body. Placenta has various roles like exchanging metabolites, nutrients, O2-CO2 transport, waste removal etc., during gestation - all of which are important for maintaining a healthy pregnancy. Placenta also acts as an endocrine organ, releasing different hormones like placental lactogen and placental growth hormone. These hormones are known to contribute to pathogenesis of GDM. There can be other genetic changes in the placenta, that can further our understanding of GDM. This review attempts to summarise the possible association of genes with GDM and their contribution to placental dysfunction, as reported in recent times.

Keywords: Dysfunction, GDM, genes, placenta, pregnancy

Introduction

Gestational diabetes mellitus (GDM) nowadays is a very common disorder of pregnant women. It was initially defined as "any degree of glucose intolerance with onset or first recognition during pregnancy."[1] The prevalence of GDM is increasing worldwide and the development of GDM is a multifactorial process that may include patient's social and demographical condition, dietary habit, genetic predisposition, ethnicity etc., GDM shares some pathophysiological similarities and dissimilarities with type 2 diabetes mellitus (T2DM). T2DM is a condition of combined target cell insulin resistance and B-cell dysfunction. Pathophysiology of GDM is still a subject of research. There is also absence of a worldwide uniform accepted diagnostic criteria for diagnosis of GDM, which may be hindering the detection and treatment of the disease. Placenta acts as a pivotal organ for maintenance of a healthy pregnancy. A healthy placenta implies proper growth and development of foetus, while morphological or functional change of placental environment can impair foetus growth. This review aims to sum up some of these morphological, anatomical, epigenetic, genetic and molecular changes of placenta in GDM patients.

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Prevalence of Gestational Diabetes Mellitus

Globally, the prevalence of GDM varies significantly. Reason behind this is the absence of any specific or worldwide accepted diagnostic criteria. According to a study performed by International Association of Diabetes and Pregnancy Groups (IADPSG), known as the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study in 2010, global prevalence of GDM is estimated up to 17.8%.[2] The most recent study is done by Saeedi *et al*. which includes an exhaustive metapopulation analysis based on IADPSG guideline criteria, the most accepted diagnosis criteria worldwide, have reported international prevalence of GDM up to 14.7%.[3] The percentage of occurrence of GDM in India falls between 3.8% and 22%.[4-6] Even higher prevalence has been reported in other parts of India, 34.9% in Punjab and 41.9% in Uttar Pradesh.[7]

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Large-scale nationwide study is needed to determine the exact prevalence of GDM in India.

Diagnostic Criteria

The very first diagnostic criteria for GDM was given by O' Sullivan and Mahan in the year 1964. The diagnostic threshold for assessing GDM was whole blood glucose levels of 90, 165, 145 and 125 mg/dl for fasting, 1-, 2-, 3-h post-glucose load respectively. There were other various recommended diagnostic thresholds available which were based on the study that included women diagnosed with diabetes mellitus after gestational period and with no proper history of adverse pregnancy outcomes.

International association of Diabetes and Pregnancy Outcome guideline

According to The International association of Diabetes and Pregnancy Outcome (IADPSG) guideline, one step 75 gm oral glucose tolerance test (OGTT) is done with the patients with recommended cutoff values given- 92, 180, 153 mg/dl for fasting, 1 and 2-hour post load, respectively,[2] based on HAPO study.[8,9]

American diabetes association guideline

There are currently two methods proposed by American Diabetes Association (ADA) for diagnosis of GDM. The one step procedure contains performing a 75 g OGTT after an overnight fast (>8 h). The patient will be diagnosed with GDM when one of the glucose values exceeds the recommended value, i.e., 92, 180, 153 mg/dl for fasting, 1 and 2 h of glucose load.

The two-step approach consists of an initial 50 g OGTT. If the 1-h plasma glucose level exceeds 140 mg/dL, a 100 g OGTT is performed as the second step. The diagnostic thresholds for the 100g OGTT are ≥95 mg/dL (fasting), ≥180 mg/dL (1-h), ≥155 mg/dL (2-h), and ≥140 mg/dL (3-h).

American council of obstetricians and gynecologists guideline

The American Council of Obstetricians and Gynecologists (ACOG) suggests screening of all woman except those with low-risk status.[10] This suggests performing a 100 g OGTT with threshold glucose values of 95, 180, 155, 140 mg/dl for fasting, 1, 2 and 3 h post glucose load, respectively.

WHO guideline

This involves conducting an OGTT using 75 g of anhydrous glucose. Blood glucose levels are measured after an overnight fast and 2 h post-glucose load. A 2-h plasma glucose level of ≥140 mg/dl is commonly used as a threshold for diagnosis. It was very much well accepted in developing countries as it is simpler than two step procedures.[11]

A uniform diagnostic criterion is needed to be formulated and accepted worldwide for proper and on-time diagnosis of GDM [Table 1].

Health Complications Associated with Gestational Diabetes Mellitus

There can be several health complications associated with GDM, occurring to both mother and foetus. The risk for newborns includes macrosomia weighing more than 4000 g, regardless of his or her gestational age. Also includes pre-eclampsia, which is defined as a high blood pressure disorder (hypertension) that can occur during pregnancy, sometime followed by fluid retention and proteinuria, which can lead to fatal conditions for both mother and the foetus [Figure 1]. Women with GDM have very high risk of developing T2DM in the future. An estimated about 10% of women with GDM have been diagnosed with T2DM just after delivery. There are several risk factors that can play role in development of future T2DM, like high glucose level, marked insulin resistance, poor β-cell function, rising level of C-peptide and falling level of adiponectin.[12] Mother with GDM can also face preterm delivery (≤37 weeks of pregnancy), primary caesarean delivery, shoulder dystocia and other labor injuries. A study by Goldman *et al*.[13] compared caesarean section delivery rate among GDM and non-GDM women, and it was 35.3% and 22%, respectively. In a population-based study as early as 1989, Jacobson and Cousins reported a higher caesarean section rate in patients with GDM compared with nondiabetic women (29.9% vs. 18.9%).[14] According to Schneider *et al*., most serious neonatal complications include macrosomia, shoulder dystocia and stillbirth.[15] Several other prenatal complications can arise like neonatal hypoglycaemia, increased neonatal percentage of body fat, increased neonatal skinfolds percentage, increased prenatal body adipose tissue content and hyperbilirubinemia. Children who have untreated GDM have a higher risk of developing T2DM at an early age.

Treatment

There are controversies about whether treatment of GDM is beneficial or not. According to a 2003 Cochrane Collaboration systematic review "there are insufficient data for any reliable conclusions about the effects of treatments for impaired glucose tolerance on perinatal outcome."[16] A study was done by Garner *et al*., that included women in 24–32 weeks gestational period and diagnosed with GDM according to Hatem *et al*. criteria and 75g OGTT and divided into two groups, either treat with strict glycaemic control or routine obstetric care.[17,18] It showed no significant differences in baby's weight, neonatal hyperglycaemia and caesarean section delivery rate between two study groups. Study by Langer *et al*. included 2775 pregnant women who were divided into groups - 555 women with GDM that was untreated, 1110 women with GDM that was treated and 1100 non-diabetic control group.[19] The result showed that rates of adverse pregnancy outcomes like neonatal macrosomia, stillbirth, neonatal hypoglycaemia and neonatal hyperbilirubinemia rates were 59%, 18% and 11% respectively in three groups, which suggests significant decrease in rate of adverse pregnancy outcomes related with GDM, when it is treated.

Table 1: Various diagnostic criteria given by some renowned organizations

Guidelines	Glucose load	Fasting glucose (mg/dl)	1-h post-glucose load (mg/dl)	2-h post-glucose load (mg/dl)	3-h post-glucose load (mg/dl)
IADPSG[2]	75g OGTT	≥92	≥180	≥153	Not required
ADA	75g OGTT	≥92	≥180	≥153	Not required
ACOG[9]	100g OGTT	≥95	≥180	≥155	≥155
WHO[10]	75g OGTT	≥126	Not Required	≥140	Not Required

IADPSG=International Association of Diabetes and Pregnancy Groups, ADA=American Diabetes Association, ACOG=American Council of Obstetricians and Gynecologists

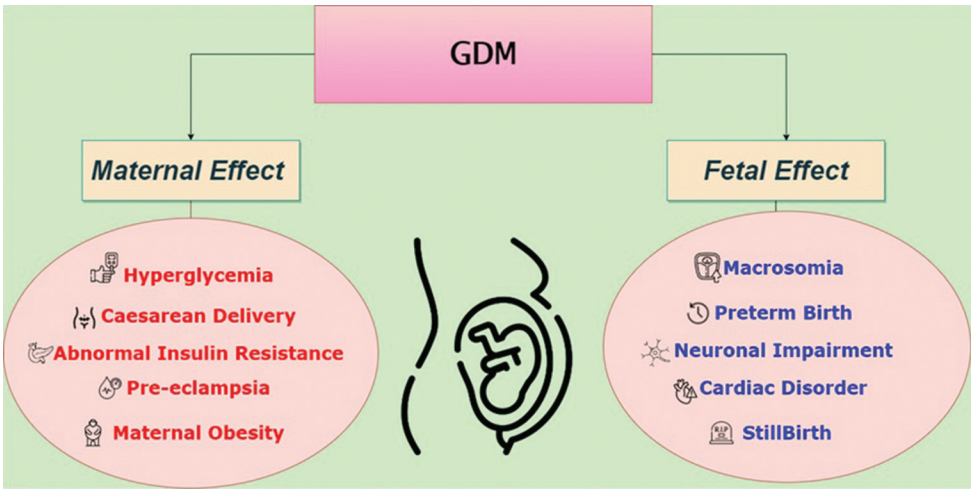

Figure 1: Gestational diabetes mellitus associated complications

The HAPO study included 25,505 pregnant women in 24 to 32 weeks of gestation.[20] 75 g OGTT was done to them and glycemic levels were studied. There were four predefined adverse pregnancy outcomes, primary caesarean delivery, neonatal hypoglycemia, cord C-peptide more than 90 percentile and birth weight. As secondary outcomes shoulder dystocia, preterm delivery, hyperbilirubinemia and preeclampsia were chosen. The study showed that frequency of primary adverse outcomes was increased parallelly with increasing maternal glucose level. This study demonstrated the direct relationship between maternal glucose levels and the health risks for both the baby and the mother.

ADA recommends consultation with a professional nutritionist and getting a personalized diet plan based on patient's BMI.[21]

Physiological, Molecular and Genetic Changes of Placenta in Gestational Diabetes Mellitus Patients

The placenta is an organ that develops in the uterus during pregnancy. It serves as a vital link between the mother and the developing fetus, facilitating the exchange of nutrients, oxygen, and waste products. It also has immunological and endocrinological functions. Placenta consists of both fetal and maternal tissue. The placenta's dynamic gene expression undergoes changes throughout pregnancy, influenced by factors such as maternal health, fetal development, and environmental cues, to meet the evolving needs of the developing fetus. The effects of GDM on placenta is documented in Figure 2.

- Physiological changes: Several studies have shown the changes of placental morphology and morpho-functionality. Placentas from GDM pregnancies are found to be larger in weight and thickness compared to healthy patient's placentas.[22] This can be correlated with macrosomia and increased nutrient demand on placenta that can lead to trophoblast cells hypertrophy and hyperplasia, increasing overall weight. Some studies have evidence of encountering small placentas and resulting reduced body weight of baby.[23] Although, placenta grows bigger or smaller, no increase or decrease in placental efficiency (BW/PW ratio) is observed.[24-26] Placental cotyledons increase in number in case of GDM.[27] The change of placenta due to GDM pathophysiology can be sex dependent.[28] Various change in chorionic villi is also observed in GDM. Terminal villi are main center for oxygen and nutrient exchange between mother and foetus. In GDM, terminal villi count is decreased and immature villi count increases, which consequently hinders the oxygen and nutrient transfer.[25] Sometime, increased fibrin deposition in the villi also obstructs oxygen transfer.[29] Evidence of edema, fibrosis and necrotic patches in patients who are treated with insulin in GDM are also there.[30] No significant change in elliptical shape of placenta is observed.[31] There is also no difference

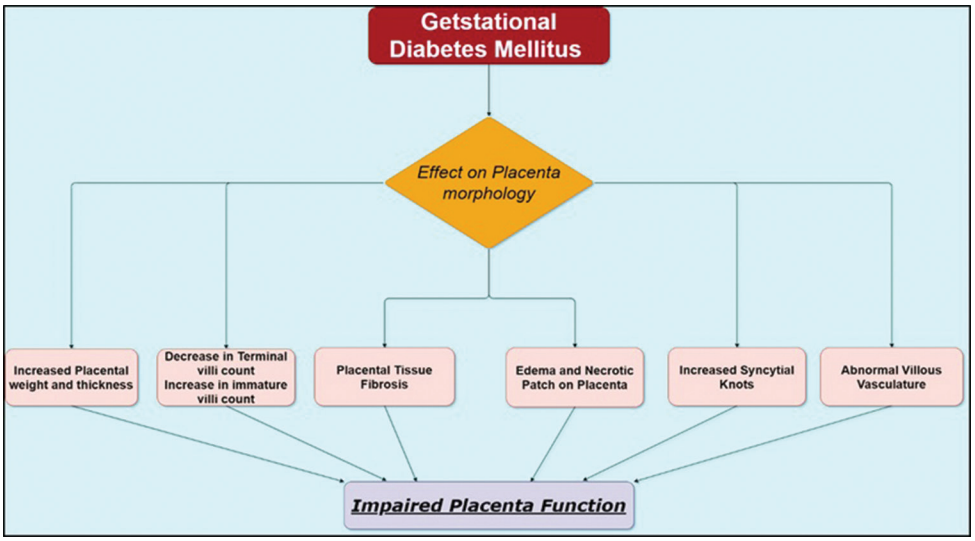

Figure 2: Effects of gestational diabetes mellitus on placenta

in cord coiling index between normal pregnant and GDM-affected women[31]

- Changes in vasculature of endothelium: Among various structural components of placenta, the vasculature of endothelium is the most affected part due to GDM. The abnormal increase, decrease or disbalance among various angiogenic factors (like Fibroblast Growth Factor-2, proliferator-activated receptor-γ, placental growth factor) that play essential role in development of microvasculature of placenta, can lead to impaired or abnormal villous vasculature development and vasculature branching and growth.[32,33] Evidence had shown increased fibroblast growth factor-2 protein expression in cord blood of patients with GDM.[34] Downregulation of various cell adhesion proteins in placenta of GDM patients leads to decrease in vascular permeability of placenta[35]
- Placental inflammation: GDM can be considered as a low-grade inflammatory condition in mother's body. There is evidence of increased circulating level of various pro-inflammatory cytokines in glycometabolic conditions like T2DM. Two evident pro-inflammatory cytokines show circulating level in GDM patients, tumor necrosis factor-alpha and IL-1β.[36] Increase of cytokines in cord blood can evidently lead to insulin resistance in GDM patients. Increased levels of adipokines and adiponectin and increased macrophage activity are also observed in the placenta. An increase in the macrophage activity can also lead to tissue damage and can introduce necrotic patches in placenta
- Molecular and genetic alterations in placenta: There are several genetic and molecular changes of placenta associated with GDM patients [Tables 2 and 3]. Here we are summarizing some of those changes and correlating with some therapeutic approaches. Exosome are extracellular vesicles secreted by all cells that carry various metabolites, lipids, proteins, nucleic acids, signaling molecules from one cell to another and mostly found in body fluids. A study has found that exosome secretion by placental trophoblast and mesenchymal cells are increased in GDM patients.[37] These exosomes are found to deliver some specific miRNAs that act upon and inhibit specific genes like INS1, which are important for proper pancreatic beta cell functioning and insulin production. Therapeutic target and removal of these exosomes can improve impaired insulin secretion in GDM patients. Galectin, a protein expressed by activated T cells, dendritic cells, eosinophils, mast cells, neutrophils, is seen to be in high concentration in placenta of GDM patients.[38] Nutrition can also alter the genetic and epigenetic environments of placenta with the perspective of nutrigenetics.[39] A study by Godfrey *et al*. showed that early diet of mother can affect the lipid metabolism of the child via various genetic changes.[40] This study focused on methylation of the promoter region of retinoid X receptor-a, which is responsible for lipid metabolism and showed increased methylation and inactivation are related to high carbohydrate intake by mother during early pregnancy. This suggests potential link between maternal diet and epigenetic changes in placenta and baby. There is evidence that the promoter region of IGF binding protein 1 and 2 (IGFBP-1,2) genes are hypermethylated in pregnant women with GDM which leads to decreased placental IGFBP1,2 expression leading to overactivation of Pi3K/AKT pathway, which causes increased glucose transport to fetus via placenta, resulting in macrosomia.[41] There is evidence of increased leptin expression in placenta of GDM affected women.[42] Due to some genetic and epigenetic alteration, downregulation of proliferator-activated receptor-α (PPARα) gene that is important for gestational gluco-lipid homeostasis in pregnant women, is observed in GDM patients.[43] A study has shown that downregulation of certain regulatory components caused overexpression of transforming growth factor beta 1 (TGFB1) and collagen type I alpha

Table 2: List of mentioned genes/RNAs/molecules upregulated in placenta of women with gestational diabetes mellitus

Genes/RNA/molecule	Probable function
Galectin-3	Inhibit glucose stress induced placental trophoblast cell apoptosis
ABHD5	Lipid metabolism and homeostasis in placenta
LRG1-ECM1	Proangiogenic effect of placenta
SF3B14 and BABAM1	Promotes ferroptosis in placental trophoblast cells
FGF-2	Promotes placental tissue fibrosis and necrosis
TNF-α, IL-1β	Low-graded inflammation
Various adipokines and adiponectin coding genes	Regulate placental metabolism and role in inflammation
Leptin	Regulate metabolism, role in obesity
Placental exosomes	miRNA delivery and INS1 gene inhibition
TGFB1 and COL1A1	Increased collagen deposition and fibrosis
CaMKIV	Placental trophoblast cell migration and invasion
Chemerin	Inhibit cGAS-STING pathway and reduce inflammation
FABP4	Increased hepatic glucose production
TXNIP	Cytotrophoblast cell migration and invasion
Gstm1, Nqo1	Oxidative stress related
Atf4, Ddit3	Protein catabolism

TXNIP=Thioredoxin-interacting protein, FABP4=Fatty acid-binding protein 4, CaMKIV=Calcium/calmodulin-dependent protein kinase IV, TGFB1=Transforming growth factor beta 1, COL1A1=Collagen type I alpha 1 chain, TNF-α=Tumor necrosis factor-alpha, IL-1β = Interleukin-1 beta, FGF=Fibroblast growth factor, LRG1=Leucine-rich alpha-2-glycoprotein-1, ECM1=Extracellular matrix protein 1

Table 3: List of genes downregulated in placenta of women with gestational diabetes mellitus

Genes/RNAs/molecules	Probable function
CircCHD2	Promotes cellular autophagy
ANXA1	Protects cell from DNA damage and damage induced apoptosis
Nk cell and T cells	Inflammation
Slc2a1, Slc16a7	Transport
Cdh1, Vcam1	Cell adhesion

1 chain (COL1A1) genes. Increased TGFB1 gene expression can cause overactivation of TGF-beta signaling pathway and COL1A1 expression causes collagen deposition and fibrosis in placental tissue, exacerbating GDM symptoms.[44] A study has found another gene, ABHD5, is overexpressed in placenta of GDM patients.[45] ABHD5 is expressed in placental trophoblast cell and code for the protein α-β hydrolase domain-containing protein 5, which has important role in lipid metabolism and homeostasis of placenta. If the exact mechanism by which ABHD5 works is revealed, ABHD5 can be used as a therapeutic target to improve lipid metabolism in GDM affected placenta, ameliorating various effect of GDM on the baby. A circular RNA, CircCHD2, is observed to be downregulated in placental trophoblast cells of GDM patients and its level is negatively correlated with blood glucose concentration.[46] CircCHD2 has a protective role towards GDM as it promotes autophagy, a cellular self-cleaning process which is important for proper functioning of placenta and when impaired, can lead to trophoblast cell dysfunction and can affect fetal growth and development. Restoring autophagy through targeted therapeutic interventions may act as a novel strategy for improving GDM and its associated complications. Study by Yao *et al*. has found two main candidate proteins that show increased expression both in gene and protein level in GDM placenta: leucine-rich alpha-2-glycoprotein-1 and extracellular matrix protein 1.[47] Therapies that can block pro-angiogenic effect of these two molecules or can cause decrease accumulation of these two molecules in placental exosomes can be used to treat complications related to GDM like macrosomia. A study of differentially expressed genes by Jiang *et al*. have validated 20 differentially expressed genes, with some upregulation and downregulation of specific genes in placenta of GDM patients.[48] The study has also shown the relation between these differentially expressed genes and given glucose load on placental cells. Ferroptosis, which is a form of cell death by accumulation of iron and increased lipid peroxidation in cells, is seen to be increased in placental tissue of GDM patients.[49] The study has also validated two responsible genes that are promoting ferroptosis in GDM affected placenta: SF3B14 and BABAM1. These can be used as therapeutic targets to decrease placental tissue damage in GDM patients. Galectin-3, which is a carbohydrate binding lectin, is observed to be upregulated in placental trophoblast cells of GDM patients.[50] The study has formulated a protective role of galectin-3 in placenta of GDM patients, as Galectin 3, in association with Foxc1, can inhibit the glucose stress induced apoptosis of placental trophoblasts. Though the exact mechanism of Galectin-3/Foxc1 pathway is still subject to research. Galectin-3 level in blood during mid-pregnancy can also act as a potential biomarker to diagnose GDM. A study has found activity of calcium/calmodulin-dependent protein kinase IV (CaMKIV), which is important for Ca2 + induced gene expression, is very much upregulated

in GDM induced mice model.[51] The study has shown that increased CaMKIV expression is correlated with decreased placental trophoblast cell migration and invasion. Thus, it can alter the placental metabolism and development in women with GDM. If the exact mechanism is known, CaMKIV can be used as a therapeutic target to decrease its deteriorating effect on placental health in patients with GDM. A study by Moreli *et al*. has compared the Annexin A1 expression in placenta tissue of GDM and non-GDM patients and showed that a decreased ANXA1 level is observed in GDM patients.[52] ANXA1 is involved in protecting the cells from DNA damage and apoptosis and is also involved in DNA damage repair mechanism. The author has previously formulated that hyperglycemia can significantly increase DNA damage.[53] Further research is needed to understand the mechanism by which ANXA1 protects cells from DNA damage and promotes DNA damage repair, so that it can be used as therapeutic target to ameliorate placental damage due to GDM and hyperglycemia. Recent studies have shown increased mitochondrial damage and dysfunction in placental trophoblast cells in patients with GDM.[54,55] Oxidative damage can be one of the most common causes promoting mitochondrial dysfunction.[56] Chemerin, which is an adipokine, increasingly expressed in placental cells of women with GDM can potentially regulate mitochondrial damage induced cGAS-STING pathway and inhibit the pathway activation and inflammation induced cell death.[57] Chemerin can be used as therapeutic target as it has protective role against placental tissue damage in GDM patients. A study by Yang *et al*., which involves single-cell RNA sequencing (scRNA-seq) for transcriptomics profiling of placental tissue in GDM patients, shows various altered gene expressions within different cell types.[58] They have found downregulation in various genes that are related to estrogen signaling, oxidative stress response etc., that may affect normal functioning of placenta. A study has found increased fatty acid-binding protein 4 (FABP4) gene expressions in biopsy of placenta tissue from GDM patients.[59] FABP4 is a co-activator of glucagon, which promotes hepatic glucose production. Increased FABP4 level can be correlated with increased blood glucose level in GDM patients and it can be used as a therapeutic target to manage GDM and hyperglycemia related adverse pregnancy outcomes. It has been found that serotonin homeostasis is important for maintaining pregnancy and placental function during gestation.[60,61] A genome-wide association studies (GWAS) by Hughes *et al*. has identified four specific loci- CDKAL1, MTNR1B, TCF7L2, CDK2NA-CDKN2B, which are associated with both T2DM and GDM.[62] These loci codes for specific proteins, when altered, can affect placental health. Study by Li *et al*. showed in a study, by QPCR and Western blotting, HIF-1α and the toll like receptor 4/myeloid differential protein-88/nuclear factor kappa-B (NF-κB) pathway is greatly increased in placenta of women with GDM.[63] In the same study, NF-kappa-B inhibitor alpha and NF-κB p65 level is also seen to be upregulated in GDM placenta. A study by Sa *et al*., thioredoxin-interacting protein (TXNIP), which is a previously established glucose sensitive gene, is seen to be upregulated in placental cytotrophoblast cells of GDM patients.[64] Investigators had used quantitative reverse transcription polymerase chain reaction, Western blotting and immunofluorescence to show higher level of TXNIP expression. However, TXNIP protein is involved in cell migration and invasion as a possible role in abnormal placenta functioning in GDM patients. Meng *et al*. experiment on hyperglycemic pregnant rats provides evidence of over 2100 gene being differentially expressed, including genes associated with oxidative stress (Gstm1, Nqo1), protein catabolism (Atf4, Ddit3), cellular transport (Slc2a1, Slc16a7) etc.[65]

Discussion

Only a limited number of genes have been assessed and confirmed to have an impact on GDM. Further research is required to identify additional genetic and molecular changes associated with the physiological alterations in the placenta of patients with GDM. However, there can be other alterations like epigenetic changes in placenta due to GDM. There are various candidate molecules like miRNA, siRNA, lncRNA responsible for epigenetic changes in placenta. miRNAs mostly have complementary sequences with either 5'UTR/3'UTR or coding sequences of the targeted mRNA. When it binds with 3'UTR or 5'UTR, it prevents the transcriptional factors and RNA polymerase to bind with the mRNA, thus causing transcriptional gene silencing. miRNA can also achieve mRNA degradation or cleaving by associating with RNA-induced silencing complex. However, miRNA can also upregulate mRNA transcription by interacting with the promoter region. DNA methylation is also another factor contributing to gene expression silencing. DNA methyltransferase caused DNA methylation, which in turn changes DNA-Chromatin interaction and prevents its transcription. While DNA acetyltransferase transcriptionally activates genes by DNA acetylation, there is evidence that global DNA methylation level in placenta is significantly increased in women with GDM compared with women without GDM.[66] Increased placental methylation can lead to silencing of various genes that can affect normal functioning of placenta in GDM. Studies showed that miRNA mediated gene silencing has a role in pancreatic beta cell functioning.[67,68] Hypermethylation in IGFBP-1,2 promoter is also observed in GDM patients, which causes overactivation of pi3k/AKT pathway, that explains occurrence of macrosomia well.[41] Various miRNA expressions are seen to be altered in placenta of GDM patients when compared to non-GDM patients, like miR-518d (upregulation), miR-96 (downregulation), miRNA-29b (downregulation), miR-144 (upregulation) etc.,[43,69-71] which can lead to not

only the dysfunction of placental tissues but also various adverse outcomes in mothers with GDM. Additional research is required to elucidate the precise underlying patterns and mechanisms of epigenetic alterations in the placenta of pregnant women with GDM. This understanding can be used to develop potential preventive measures and therapeutic interventions.

Conclusion

GDM and consequent hyperglycemia can severely affect placental physiology, chemical environment, genetics and epigenetics. Placenta serves various function that is essential for proper foetal development, like oxygen-carbon-di-oxide exchange (acting as foetus' lungs), serving the foetus with various essential nutrients necessary for its growth, acting as a disposal and removal center of waste material coming from foetus as well as a barrier that prevents transfer of various bacteria, virus and pathogens. GDM can lead to alterations in placental physiology and functionality, potentially resulting in compromised placental function and inadequate foetal growth and development, leading to various adverse foetal outcomes.

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Author contributions

- AM and BKD wrote and proofread the review article
- SC supervised the article
- SM conceptualised the whole review article.

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Conflicts of interest

There are no conflicts of interest.

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