Review Article

The placental metabolic derangements and fetal complications in Gestational Diabetes Mellitus: A Literature Review

Abstract

Gestational diabetes mellitus (GDM) is associated with adverse maternal and fetal complications including longer-term risk for developingT2DM, obesity and cardiovascular complications (CVD) later in their life. The placental derangements play a major role in the pathobiology of GDM. This review is aimed at to discuss the various aspects altered placental pathways in GDM, and where there are gaps in the literature that warrant further exploration.Published scientific manuscripts between 2000 and 2022 that discussed the role of insulin resistance, dyslipidaemia, oxidative stress and low-grade inflammation in the pathogenesis of GDM were reviewed. The main keywords used were insulin resistance, oxidative stress, lipid metabolism, dyslipidaemia, and low-grade inflammation. GDM is associated with maternal insulin resistance, dyslipidaemia, oxidative stress, and inflammation. These maternal derangements in GDM could affect placental and foetal lipid metabolism. The altered placental pathways could enhance the transfer of nutrients like glucose and FFA to the growing foetus causing overgrowth and adiposity. GDM foetuses experienced oxidative stress and inflammation and they could be involved in foetal programming for future metabolic diseases such as T2DM, obesity, CVD, etc. Understanding the various molecular mechanisms of placental derangements involved in the pathogenesis of GDM could expand our vision and open up avenues for therapeutic and preventive strategies for the better management of GDM women.

Keywords: Insulin signalling; dyslipidaemia; oxidative stress; inflammation

Highlights:

- Gestational diabetes mellitus is associated with adverse maternal and fetal complications
- Placental derangements are involved in pathogenesis of Gestational diabetes mellitus
- Understanding of these derangements is warranted to develop newer treatment.

Introduction

The International Diabetic Foundation (IDF) has estimated that one in six pregnancies is affected by hyperglycaemia and 84% of them is due to gestational diabetes mellitus (GDM) and the remaining 16% is due to type 2 diabetes mellitus(T2DM) (2,3). Gestational diabetes mellitus (GDM) is defined as maternal hyperglycemia first developed or detected during gestation(4). Gestational diabetes mellitus affects about 13% of pregnant women worldwide(3).The prevalence of GDM among Indian pregnant women is around 20 % using the International Association of Diabetes and Pregnancy Study Groups criteria (IADPSG) and is likely to increase with the increment in obesity epidemic. The GDM occurrence is increased in parallel with the increase of T2DM in India (5).

During early pregnancy there is an increased insulin sensitivity to promote storage of the maternal glucose into adipose tissue for the energy demands of later pregnancy (6). As pregnancy progresses, there is a surge of hormones such as progesterone, estrogen, cortisol and placental hormones such as placental growth hormone, and placental lactogen together to favour a mild state of insulin resistance in normal pregnancy. Further, mild insulin resistance at late pregnancy causes slight increase in the maternal glucose and free fatty acid (FFA) levels for ready transport across the placenta to fuel the fetal growth. There is an increased hypertrophy and hyperplasia of pancreatic beta-cells to compensate for insulin resistance developed at late pregnancy. However in GDM, hyperglycemia is heightened as a result of beta-cell dysfunction along with chronic insulin resistance (8).

Gestational diabetes mellitus is associated with maternal insulin resistance, dyslipidemia, oxidative stress and inflammation. Maternal hyperglycemia and dyslipidemia have been reported and correlated with fetal growth in GDM. In addition to that, maternal hyperglycemia causes an increase in oxidative stress in maternal as well as in placenta of GDM women(9). Further increased maternal pro-inflammatory cytokines such as TNF- α and leptin and decreased anti-inflammatory cytokine adiponectin were reported in GDM. These maternal derangements could favour the increased placental transport of glucose and free fatty acids to the fetus resulting in fetal overgrowth. However the molecular mechanisms at the placental level are still unknown.

The placenta is the barrier between the maternal and fetal environments and is also exposed to hyperglycemia and its consequences during GDM. This can influence the transport of glucose, amino acids, and fatty acids across the placenta. Post-receptor defects are reported in the insulin signaling pathway in the placenta of women with pregnancies complicated by

diabetes and obesity(10). Recently, it has been shown that placental lipid metabolism and their related genes are altered in diabetic pregnancies(11). Studies report increased triacylglycerol (TG) accumulation in the placenta of diabetic women and rodent diabetic model. However, there is only limited information about the underlying mechanism of increased placental TG accumulation and the regulation of placental-fetal lipid fluxes in GDM. Altered placental insulin signalling and lipid metabolism have been emerging as key mechanisms in the pathogenesis of gestational diabetes mellitus. However, the molecular mechanisms are still unclear. This review was aimed to understand the various aspects of altered placental pathways involved in pathobiology of GDM and where there are gaps in the literature that warrant further exploration.

Prevalence and risk factors of Gestational Diabetes Mellitus

Gestational diabetes mellitus affects nearly 13% of pregnant women worldwide (3). The prevalence of GDM among Indian pregnant women is around 20% using the International Association of Diabetes and Pregnancy Study Groups criteria (IADPSG) and this number is expected to increase with the increment in obesity epidemic. Several risk factors for GDM have been identified consistently. They are, overweight / obesity, advanced maternal age, family and personal history of GDM, first degree relatives with diabetes, excessive gestational weight gain, ethnicity, genetic polymorphisms, westernized diet and other diseases of insulin resistance like polycystic ovarian syndrome. BMI, caloric consumption, and nutritional pattern are independently associated with GDM.

Maternal Glucose Metabolism in Gestational Diabetes Mellitus

Impaired insulin secretion and chronic insulin resistance are the main metabolic factors involved in the pathogenesis of GDM pregnancy. However, low-grade inflammation and oxidative stress are also known to affect the insulin signalling pathway and cause insulin resistance.In response to chronic hyperglycaemia, there is a prolonged and excessive insulin secretion resulting in β-cell dysfunction (26). However, the underlying mechanisms of β-cell dysfunction in GDM are complex and unclear. β-cell dysfunction is worsened by insulin resistance. In insulin-resistant conditions, there is a reduced insulin-mediated glucose uptake which leads to hyperglycaemia, overloading the β-cells to secrete additional insulin in response. This glucotoxicity causes β-cell dysfunctionin diseases like GDM. Further, chronic glucotoxicity causes β-cell apoptosis over time (27). Studies reported that β-cell number or mass are essential factor of β-cell function (28). Reduced β-cell hyperplasia also reported in

animal studies and suggested that it may have a role in GDM. Thus, an inadequate β-cell mass, decreased β-cell number and β-cell dysfunction contributes to the pathogenesis of GDM.

In GDM, insulin resistance may occur when there is an impaired response to the insulin with its receptor or a defective insulin signalling intermediates. Studies reported elevated levels of cytokines and pregnancy-specific hormones alter the expression of insulin signalling proteins. Defective insulin signalling causes decreased translocation of glucose transporter 4 (GLUT4) to the plasma membrane by which the glucose enters into the cell. There is a reduced insulin-stimulated glucose uptake in GDM women compared to normal pregnancy. Studies reported that, expression or activity of downstream molecules of insulin signalling pathway such as IRSs, PI3K, and GLUT4 are altered in adipose tissue and skeletal muscle of GDM women (30). Many of these molecular events persist beyond pregnancy (31). These molecular changes create generalized and local insulin resistance in various tissues and organs of GDM women. However, the role of the placenta in the pathogenesis of GDM is poorly understood and only a few studies were conducted on the placental insulin signalling and its effect on fetal growth.

Placental Insulin Signalling in Gestational Diabetes Mellitus

In a normal pregnancy, IR is expressed in the trophoblast cells in the early gestational period. However, as the pregnancy progresses into the late trimester, the amount of IR expression gets limited in the trophoblast cells and increases in expression in the fetal endothelial cells. The amount of IR expression can be modulated by the types of treatment used and metabolic control. GDM women only on medical nutrition therapy had shown a decreased placental trophoblast IRs whereas, insulin-treated GDM women showed an increase in trophoblast IRs expression. In GDM, the levels of expression of IR in placental trophoblast cells depend on the metabolic control of the mothers. IR expression is decreased in poorly managed or untreated GDM women, whereas no change has been observed in the optimally controlled GDM women. Differential expressions of downstream molecules of the insulin signalling pathway are observed in the GDM placenta. These alterations are more pronounced when obesity co-exists with GDM. A reduction of IRS1 expression is a common feature in skeletal muscle and adipose tissue in women with GDM (32).

Decreased placental protein expressions of IRS1 and PI3Kp85α and increased PI3Kp110α are reported in insulin-controlled non-obese women with GDM compared to normal pregnant mothers and diet-controlled GDM mothers (33). Placental GLUT-4 mRNA and protein expressions are decreased in non-obese insulin controlled GDM compared to non-obese controls (33).

Oxidative stress in Gestational Diabetes Mellitus

In gestational diabetes mellitus, altered glucose tolerance and insulin resistance result in hyperglycaemia. Hyperglycaemia is directly implicated in the formation of free radicals by various pathways, which leads to oxidative stress in gestational diabetes mellitus (34). Recent studies have shown that there was an increased maternal plasma, cord plasma, and placental MDA levels in gestational diabetes mellitus compared to normal pregnant women(36). Several other studies have also found evidence for lipid peroxidation, using a variety of appropriate assays comprising 8-Isoprostane, 4-hydroxynonenal (HNE) and thiobarbituric reactive substance (TBARS) (37,38). In diabetic pregnancies increased levels of TBARS (39) and LOOH (40) have been reported. Women with GDM are shown to report an increase in the level of 8- Isoprostane compared to normal pregnant women (41).Maternal α-tocopherol(45) and vitamin C levels (46) are lower in GDM women when compared to normal pregnant women. Conflicting results about maternal plasma SOD and catalase activity are reported in GDM pregnancy (34). Maternal Glutathione peroxidase activity is unchanged (47) or lower (48) in GDM women compared to control pregnant women. Increased maternal serum glutathione S-transferase levels in patients with GDM are reported in comparison with normal pregnant women (49).Increased oxidative stress and impairment of antioxidant defense have been reported in maternal, cord plasma and placenta of women with gestational diabetes mellitus (41,50).

Placental Oxidative stress in Gestational Diabetes Mellitus

Reactive oxygen species (ROS) in pregnancy is required for normal embryonic and fetal development. Increased and sustained ROS production affects placental function and fetal growth, resulting in the priming of future diseases in the offspring (51,52). The increase in ROS, together with the impaired antioxidant activity is related to the induction of congenital malformations in pre-gestational diabetic pregnancies (53). In the gestational diabetic placenta, there is increased oxidative stress compared with healthy pregnant

women (54). However, the simultaneous increase in antioxidant enzyme activities compensates for the increased placental oxidative stress (55,56).

Increased oxidative stress or TNF-alpha triggers the activation of JNK and p38 MAPK resulting in cell death. Activation of p38 MAPK also influences cellular processes such as cell growth, apoptosis, response to stress by altering gene expressions, inflammation, immunity, cytoskeletal rearrangement and other signalling pathways such as insulin signalling, NF-kB, etc. Chronic activation of the p38 MAPK pathway is associated with ischemia-reperfusion injury, inflammation and neuronal disease (59). Excessive ROS production could cause changes at the micro-anatomical and molecular levels in placental tissues.

The activated Nrf2/ARE pathway leads to the induction of numerous genes encoding antioxidant and phase-2 detoxifying enzymes and related proteins. In this role, Nrf2/ARE activation is one of the main defense mechanisms against oxidative stress in cells and tissue. Dysregulation of Nrf2 is involved in the etiology of diabetes and its complications (60,61). Placenta of women with pre-existing type 2 diabetes showed a decreased expression of Nrf2 and thereby decreasing the expression of hemoxygnase-1 (62). The placenta of gestational diabetic rats and pre-gestational diabetic mice showed an increased Nrf2 expression (63,64). Increased Nrf2 expression has a protective role in diabetic cardiomyopathy (65) and diabetic nephropathy (66). However, the placental Nrf2 expression and its relationship with antioxidant enzyme expression in gestational diabetes need to be explored.

Maternal Lipid Metabolism in Gestational Diabetes Mellitus

Most of the studies observed maternal hypertriglyceridemia in GDM women when compared with a normal pregnancy in all trimesters of pregnancy. Other plasma lipid parameters such as total cholesterol, HDL-cholesterol and LDL-cholesterol levels have been reported to be very variable in GDM women when compared to normal pregnant mothers (67). However, small and dense LDL particles are the representative of an insulin-resistant state and is increased in GDM women. They are consistently associated with future cardiovascular complications in GDM women (68,69). Further, plasma TAG levels are associated with the levels of estradiol, progesterone, and prolactin in the pregnancy. Increased levels of FFAs during late pregnancy can also lead to insulin resistance in normal pregnancy. However, there

is an elevated maternal FFAs level than the normal pregnant women are reported in GDM women (71).

Maternal hyperglycaemia contributes to fetal macrosomia by increasing substrate availability, stimulating excessive growth and adiposity (72). Macrosomia is also observed even in newborns of diabetic mothers with satisfactory glycemic control; this suggests that substrates other than glucose could contribute to the excess fat deposition in fetal adipose tissue. Maternal plasma FFA could undergo transplacental transfer and get deposited as triacylglycerols in fetal adipocytes. Several clinical studies have documented that elevated maternal plasma triacylglycerol levels account for fetal fat accretion (73). Hence the hyperglycaemia and hypertriacylglycerolmia of the diabetic mothers are significant factors to enhance substrate availability to the fetus.

Placental Lipid Metabolism in Gestational Diabetes Mellitus

A recent study reported that preferential activation of genes of placental lipid transport; storage and mobilization are observed in the GDM placenta compared to the T1DM and control placenta. Further, the authors stated that fatty acids are the main energy substrate for the placental cells rather than glucose (74). TAG and phospholipids are higher in placenta of diabetic women when compared to the normal placenta. Fatty acid synthase is a key enzyme of fatty acid synthesis; its protein expression is increased in the GDM placenta compared to the normal placenta (75). Stearyl CoA desaturase introduces double bond in the fatty acids and is involved in TAG storage. Its mRNA expression is up-regulated in GDM placenta than the control placenta (74). Further increased placental TAGs are stored as lipid droplets in the syncytiotrophoblast. This suggests that most of the fatty acids in lipid droplets are derived from the maternal circulation. However, the exact mechanisms of FFA derived from the lipid droplets and its transfer into fetal circulation are yet to be explored.

Association of Insulin Resistance, Oxidative Stress, Inflammation, Lipid Metabolism and Maternal / Foetal outcome in GDM

Chronic insulin resistance and beta-cell dysfunction are the key metabolic factors in the pathogenesis of GDM. Maternal hyperglycaemia leads to increased ROS production and causes oxidative stress in GDM (76). Increased maternal oxidative stress can activate NFκB and JNK pathway and produces pro-inflammatory cytokines. Increased levels of pro-inflammatory cytokines and low-grade inflammation were reported in GDM (77).Studies

reported that early trimester elevated pro-inflammatory cytokines such as TNF-α and leptin and decreased anti-inflammatory cytokine adiponectin levels were associated with the increased risk of GDM . Maternal dyslipidaemia is associated with insulin resistance and inflammation in GDM. Dyslipidaemia in early trimester is associated with the increased risk of developing GDM in pregnant women (78). Therefore, maternal insulin resistance, oxidative stress, inflammation, and dyslipidaemia are interlinked and involved in the pathogenesis of GDM.

The maternal pro-inflammatory cytokines and ROS activate the placental NF-κB pathway and impair the insulin signalling pathway by serine phosphorylation of IR-β and IRS. Studies reported that GSK3 attenuates the insulin signalling by causing the serine phosphorylation of IRS1 (79). We found increased placental expression of GSK-3 in GDM women. Studies reported that GSK-3 activates the NF-κB pathway by phosphorylating the NEMO. Further, GSK-3 inhibits the Nrf-2/ARE pathway by phosphorylating Nrf2 in a specific manner and degrades it. Nrf-2 increases the antioxidant enzymes and thereby inhibits the oxidative stress-mediated NF-κB activation. Hence, we suggest that increased GSK-3 protein expression in the GDM placenta is associated with placental insulin resistance, oxidative stress and inflammation and in the pathogenesis of GDM.

Increased maternal glucose and TG would favour a state of glucolipotoxicity in the GDM placenta. Further, increased placental transport of glucose and FFA produces more ROS and results in placental oxidative stress. We found increased placental protein expressions of Nrf2 and antioxidant enzymes catalase and SOD1 in GDM women. Studies reported that GDM placentas were less responsive to oxidative stress and inflammatory cytokines in in-vitro conditions (80). These observations suggest that GDM placentas are better adapted and to prevent from the heightened maternal oxidative stress and inflammation.

Increased placental glucose and FFA are stored as TG in the placenta and hydrolysed for later release into the foetal circulation. A recent study has reported that PI3K inhibitor reduces lipid accumulation in primary goose hepatocytes by decreasing the LXRα expression and increasing the PPAR expression (81). In our study, we found increased placental expression of PI3K p110α and lipogenic proteins such as LXRα, FAS, and SCD1 and decreased lipolytic protein PPARα. We demonstrated placental lipid accumulation in GDM women. These observations suggest that increased PI3K p110α might be associated with the placental lipid accumulation in GDM women. Studies reported that increased adipose tissue lipid

accumulation leads to the increased secretion of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. Further, these pro-inflammatory cytokines activate JNK and NF-κB pathways and cause insulin resistance (82). Therefore, we conclude that altered expressions of placental insulin signalling pathway proteins are associated with oxidative stress, inflammation, and lipid accumulation in GDM.

The altered placental pathways could enhance the transfer of nutrients such as glucose and FFA to the growing foetus. Studies reported that increased nutrient level favours the foetal adiposity and macrosomia in GDM newborns (83). The short term consequences of GDM are related to foetal adiposity. However, the intrauterine hyperglycemic environment will lead to oxidative stress and inflammation and is involved in foetal programming for future T2DM, obesity, CVD, etc (84).

The schematic representation of possible molecular mechanisms of association of insulin resistance, oxidative stress, inflammation, lipid metabolism, and maternal-foetal outcomes are illustrated in Figure 1.

Conclusion

GDM is associated with maternal insulin resistance, dyslipidaemia, oxidative stress, and inflammation. These maternal derangements in GDM could affect placental and foetal metabolism. The altered placental pathways could enhance the transfer of nutrients like glucose and FFA to the growing foetus causing overgrowth and adiposity. Further, GDM foetuses experienced oxidative stress and inflammation and they could be involved in foetal programming for future metabolic diseases such as T2DM, obesity, CVD, etc. Better understanding of these derangements and their contribution to GDM is warranted in order to develop effective treatments and prevention strategies.

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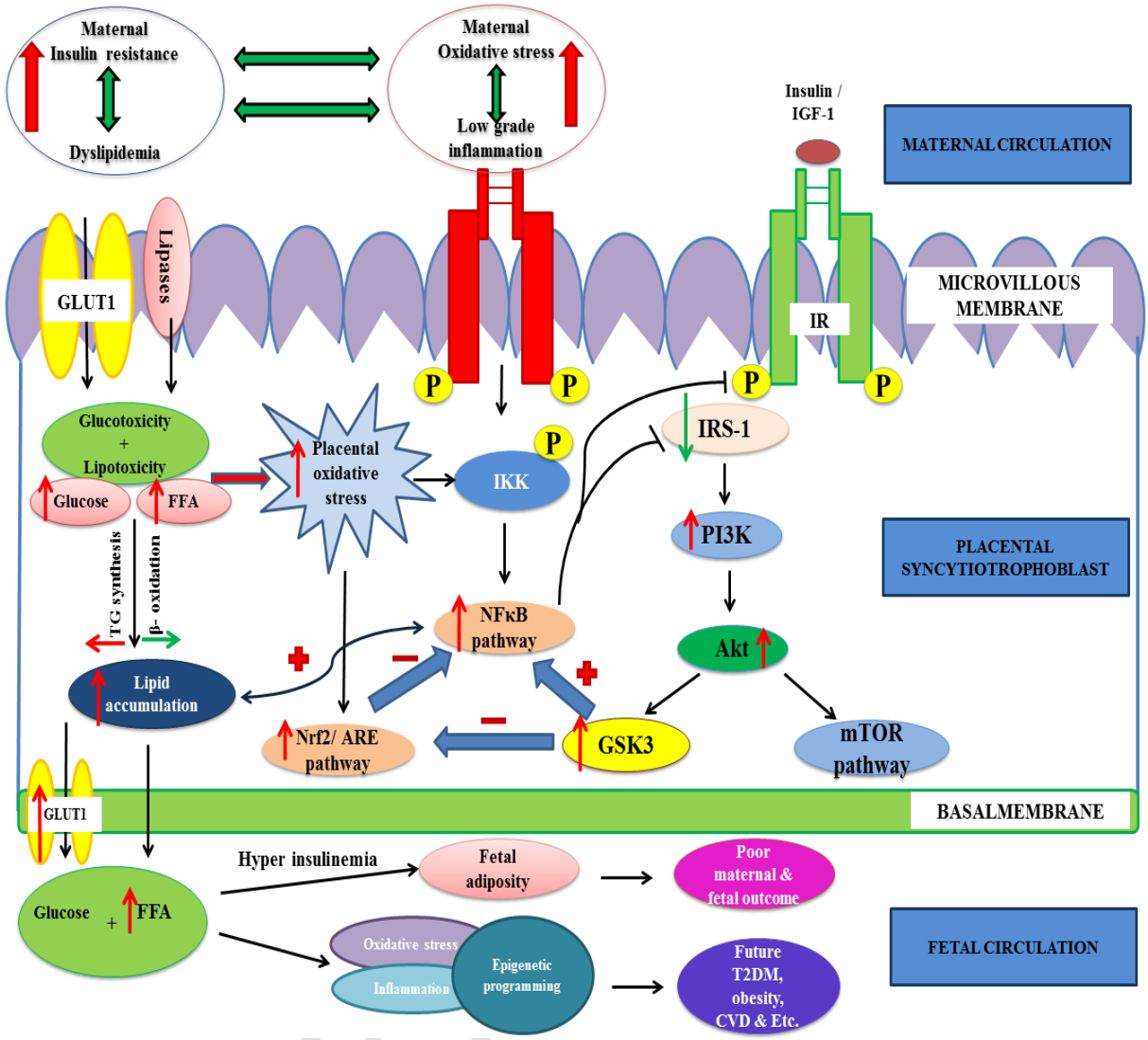

Figure 1. Possible molecular mechanisms of association of insulin resistance, oxidative stress, inflammation, lipid metabolism, and maternal-foetal outcomesin GDM women. IGF-1 – Insulin-like growth factor-1, GLUT – Glucose transporter, IR – Insulin receptor, IRS1 – Insulin receptor substrate-1, PI3K – Phosphatidylinositol-3 kinase, GSK3 – Glycogen synthase kinase, Nrf-2 - Nuclear factor erythroid 2–related factor 2, ARE - Antioxidant response element, IKK - IκB kinase, NF-κB - Nuclear Factor-κB, FFA –Free fatty acid, T2DM – Type 2 diabetes, CVD – Cardio vascular diseases.