Journal of Complementary Medicine Research, ISSN: 2146-8397 Vol. 14, No. 5, 2023 (pp. 29-56)

RESEARCH ARTICLE WWW.JOCMR.COM

Diabetes during Pregnancy – A review

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❖ **Abstract**

Despite significant improvements in the treatment of diabetes mellitus, both pregestational (PGDM) and gestational diabetes (GDM) represent a danger to the embryo, foetus, and pregnancy. Congenital abnormalities, particularly those of the heart, neurological system, musculoskeletal system, and limbs, may be more common in people with PGDM. PGDM can cause macrosomia in the foetus, but it can also restrict foetal development in the face of severe maternal problems, such as nephropathy. Stillbirth and perinatal mortality, cardiomyopathy, respiratory illness, and perinatal asphyxia are among possible perinatal consequences of PGDM. GDM, which usually appears in the second part of pregnancy, causes comparable but less serious issues. Their severity increases with earlier development of GDM and is inversely proportional to glycemic control. Early GDM commencement may result in an increase in the risk of congenital abnormalities. Both PGDM and GDM can lead to a variety of motor and behavioural neuro developmental issues, such as an increased risk of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). With better diabetes management, the incidence and severity of most complications decreases. Hyperglycemia in the mother and foetus, increased oxidative stress, epigenetic alterations, and other, less well-defined pathogenic processes are all linked to diabetic-induced harm in pregnancy.

❖ **Key words**
pregestational diabetes, gestational diabetes, pregnancy, anomalies, growth disturbances, perinatal complications, neuro developmental problems, diabetic control

DOI: 10.5455/jcmr.2023.14.05.4

1) Introduction

Prior to the discovery of insulin, the major therapy option for diabetes moms was a strict low-carbohydrate diet. Liveborn newborns were commonly of low birth weight during the period. The goal of this limited diet was to not only regulate maternal blood glucose levels, but also to avoid or reduce the high risk of preterm delivery. The only option to lower blood glucose levels and avoid intrauterine foetal mortality or severe diabetes complications with placental damage was to starve the mother. Everything appears to be different now, but we still have a long way to go before we can be really satisfied. Type 1 or type 2 diabetes mellitus (T1DM or T2DM) has progressively grown in women of reproductive age, now accounting for around 1% of all pregnancies. Diabetes mellitus that develops in a woman before to pregnancy (pregestational diabetes mellitus—PGDM) can have a number of negative consequences for the mother, foetus, child, and the pregnancy itself.

Poorly regulated PGDM before to conception and throughout the first trimester of pregnancy is linked to a higher risk of significant congenital deformities, spontaneous abortions, stillbirth, and perinatal death. [1, 2, 3, 4, 5]

PGDM has also been linked to a variety of pregnancy difficulties as well as neurological issues in the children. Furthermore, long-term consequences of insulin resistance in kids may raise the risk of cardiovascular disease, hypertension, and diabetes (metabolic syndrome).

Over the last 20 years, the prevalence of gestational diabetes (GDM), which generally occurs in the second part of pregnancy, has grown dramatically. Depending on ethnic background, maternal age, and diagnostic criteria, current incidence rates range from 1.7 to 15.7 percent. [6, 7]

Increased maternal and neonatal mortality, perinatal problems, and neurodevelopmental delay are all possible side effects of GDM. [7, 8]

The potential for both PGDM and GDM to interfere with foetal development, resulting in higher birth weight, is worth noting (macrosomia). The degree of glycemic control has a direct relationship with the rate and severity of the above-mentioned problems. Complications will be minimised if you have complete control. [1, 9]

Early diagnosis of PGDM and/or GDM, regular medical follow-up to detect problems early, strict glycemic management, and early identification of women at risk for complications are all critical. Reduced rates of congenital abnormalities and neurodevelopmental issues, improved foetal survival, normal birth weight, and minimum negative effects on mother and foetal health will all result from optimal management. [10, 11, 12, 13, 14]

We will cover the consequences of maternal diabetes in pregnancy (both PGDM and GDM) on embryonic and foetal health, newborn infant health, and long-term neurodevelopment in this review. In order to ease the many diabetes issues addressed here, we will strive to stress the need of proper glycemic management. The etiology and pathophysiology of diabetic embryopathy, as well as approaches to improve therapy, are outside the scope of this clinical study.

2) Congenital Malformations and Diabetes in Pregnancy

When compared to nondiabetic pregnancies, PGDM is associated with a considerably higher risk of many types of serious congenital abnormalities, including a greater than 10-fold increase in some specific, very rare birth disorders. [15]

Glycemic management during the first trimester of pregnancy is related with the most severe foetal embryopathy, as well as higher levels of maternal glycosylated haemoglobin (HbA1c). [16]

The most prevalent congenital abnormalities in children born to moms with PGDM are cardiac anomalies, which account for around 40% of all malformations, as well as limb, neural tube, and musculoskeletal problems. [17, 9]

Atrioventricular septal (AVS) abnormalities, hypoplastic left heart syndrome, and persistent truncus arteriosus are the most common cardiac malformations associated with PGDM. [15, 18, 19, 20, 21]

During the first trimester, PGDM is also linked to a greater foetal heart rate. [22]

Tobacco smoking during pregnancy complicated by PGDM increases the diabetes effects on preterm delivery and congenital malformations, particularly atrial septal defects, probably due to tobacco smoking's unfavourable influence on glycemic management. [23]

Tinker et al. assessed the connection between PGDM and GDM and a variety of particular congenital abnormalities in a nationwide birth defects prevention research based on data gathered in the United States between 1997-2011.They discovered a statistically significant elevated risk of PGDM in 46 of the 50 birth abnormalities studied, with point estimates ranging from 2.5 to 80.2. Sacral agenesis (aOR, 80.2; 95 percent confidence interval, 46.1–139.3), holoprosencephaly (aOR, 13.1; 95 percent confidence interval, 7.0–24.5), longitudinal limb deficiency (aOR, 10.1; 95 percent confidence interval, 6.2–16.5), heterotaxy (aOR, 12.3; 95 percent confidence interval, 7.3–20.5), persistent truncus arteriosus (aOR, 14.9; They also found significantly weaker links between GDM and birth abnormalities in 12 of the 56 anomalies studied, with odds ratios ranging from 1.3 to 2.1, the majority of which were cardiac. [15]

Several studies have distinguished between the newborn outcomes of mothers with various kinds of diabetes. Pregestational type 1 diabetes was linked to more severe neonatal morbidity, preterm delivery (RR 3.32; 95 percent CI 3.14–3.51), and fetal overgrowth (RR 8.05; 95 percent CI 7.41–8.75) in a population-based study of diabetes throughout pregnancy in Spain (2009–2015). [24]

In a large cohort of Chinese women with impaired fasting glucose (847,737 women) and diabetes (76,297 women), Wei et al. compared the rate of birth defects diagnosed before birth, such as anencephaly, hydrocephalus, open spina bifida, cleft lip, cleft palate, congenital heart disease, and trisomy 21, to controls (5,523,305 women). Birth malformations were substantially more prevalent in women using PGDM (OR 1.48, 95 percent confidence interval 1.15–1.91) compared to controls (OR 0.95, 95 percent confidence interval 0.85–1.05). [25]

The scientist investigated the incidence of congenital abnormalities and severe perinatal outcomes in GDM in a French research based on data from all births in France in 2012. They discovered that children born to mothers with insulin-treated GDM had a higher risk of cardiac abnormalities (OR 1.3 [95 percent CI 1.1, 1.4]) than those born to women with diet-treated GDM. They also discovered an unexpectedly high rate of foetal death in the GDM group (OR 1.3 [95 percent CI 1.0, 1.6]), which they believe is attributable to undetected PGDM. [26]

Other studies have recently shown that kids of GDM mothers had a higher prevalence of congenital abnormalities. [27, 28]

Zawiejska et al. analysed obstetric data of 125 women without PGDM who were considered to have an elevated risk of developing GDM based on Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria or had fasting glycemia levels greater than 5.1 mmol/dL during the first trimester. They discovered that early fasting glycemia, which is diagnostic for GDM (according to IADPSG criteria), is linked to a higher risk of congenital anomalies, particularly cardiac malformations. These pregnant women did not have a diagnosis of hyperglycemia before pregnancy. [27]

In a study of 29,211,974 live births in the United States, Wu et al. looked at the relationship between PGDM and GDM and 12 subtypes of congenital abnormalities in newborns. With an adjusted relative

risk (aRR) of 2.44 (95 percent CI 2.33–2.55) for PGDM and 1.28 (95 percent CI 1.24–1.31) for GDM, they found an increased risk of congenital abnormalities at birth. [28]

Despite the fact that maternal hyperglycemia is the principal teratogen in all diabetes pregnancies, the underlying mechanisms by which hyperglycemia exerts its teratogenic effects are yet unknown. Fetal hyperglycemia is caused by maternal hyperglycemia, and the severity of foetal embryopathy is determined by the intensity and time of the exposure, as well as genetic susceptibility and metabolic variables. Hyperketonemia, enhanced arachidonic acid metabolism, myoinositol, and prostaglandins metabolism are some of the other hypothesised processes and causes. In diabetic embryopathy, hypoxia and elevated oxidative stress have also been implicated. [9, 29, 30, 31]

3) The Effects of Diabetes on Intrauterine and Postnatal Growth

3.1) Growth Disturbances in Newborn Infants of Diabetic Mothers

Fetal growth is a complicated multi-step process that is influenced by mother substrate supply, uterine environment, and yet-to-be-discovered maternal and foetal hormonal pathways. Maternal nutrition, metabolism, maternal sickness, and placental function all play key roles in foetal development and growth, which affects the child's and adult's health and disease. [8, 9, 32, 33]

Many prenatal and postnatal environmental variables (such as the severity and start of diabetes, the degree of diabetes management, and treatment regimens) may have an impact on the growth of diabetic mothers' kids. Nutrition, the family environment, health condition, and other postnatal variables all impact the growth of a diabetic mother's kids.

Due to maternal hyperglycemia, maternal PGDM and GDM are risk factors for excessive foetal development (macrosomia). [8, 9, 34, 35]

Fetal macrosomia affects 15–45 percent of children born to diabetes moms and is three times more common than in normoglycemic non-diabetic mothers. [36]

It all relies on how well you manage your diabetes. Macrosomia is diagnosed when a full-term infant's birth weight exceeds 4000 grammes or when the 90th percentile is exceeded at any gestational age. [37]

Due to the buildup of subcutaneous fat in the abdomen and interscapular regions, foetal macrosomia in diabetes pregnancies is characterised by bigger shoulder and extremity circumferences, a lower head-to-shoulder ratio, considerably higher body fat, and thicker upper-extremity skin-folds. [38, 39, 40]

Macrosomia is initially detected by ultrasound around week 24 of pregnancy and is usually present throughout the pregnancy. [40]

Fetal macrosomia has been linked to an increased risk of perinatal death, Erb's palsy, shoulder dystocia, brachial plexus injuries, and newborn morbidity, as well as being a source of severe maternal difficulties during birth that may endanger the mother's life. [9, 33, 41, 42, 43, 44, 45, 46, 47]

In diabetes pregnancy, the increased risk of macrosomia is mostly owing to the mother's higher insulin resistance, which also contributes to maternal hyperglycemia and dyslipidemia. [39, 48]

Maternal glucose levels beyond a certain threshold boost the fetus's ability to absorb nutrients through the placenta, resulting in macrosomia. [36]

The maternal-derived or exogenously supplied insulin, on the other hand, does not cross the placenta, and the foetus responds to maternal hyperglycemia with hyperinsulinemia, which lowers foetal blood glucose levels, increases foetal fat tissue, and promotes development. [39]

3.2) Factors Contributing to Fetal Growth

Pregnancy, in general, initiates a number of maternal adaption mechanisms that ensure a metabolically healthy embryo's ontogeny and development. One of the key pregnancy adaptation processes that occurs via functional changes and increasing -cell mass is the reversible expansion of maternal insulin secretion and progressive insulin resistance. [49, 50, 51, 52]

The placenta is important in the development of temporary insulin resistance during pregnancy, which returns to normal following birth. The release of hormones, cytokines, adipokines, and other chemicals from the placenta to the maternal circulation mediates insulin resistance. [53]

Human chorionic gonadotropin (hCG), human placental lactogen (hPL), and human placental growth hormone (hPGH) are hormones secreted by the placenta that bypass the regular hormonal regulation circuits. [54, 55]

Hepatic gluconeogenesis and lipolysis are boosted by placental lactogen and growth hormone, and maternal insulin-like growth factor I (IGF-1) levels rise in response to increasing growth hormone levels. PGH (placental growth hormone) is a key regulator of maternal insulin-like growth factor I (IGF-I) (IGF-I). [56]

Increased IGF-I, IGF-II, IGF-IR, and IGF-IIR mRNA levels in the placenta are linked to foetal macrosomia. [57]

Increased insulin resistance is connected with an increase in the levels of pregnancy-related hormones such as oestrogen, progesterone, cortisol, and placental lactogen in the maternal circulation. This normally happens between the 20th and 24th week of pregnancy. [58, 59, 60]

Adipocytokines, such as leptin, adiponectin, tumour necrosis factor (TNF), interleukin-6, resistin, visfatin, and apelin, are also produced by adipose tissue. [61, 62]

These have a role in glucose homeostasis, which can lead to insulin resistance in pregnant women. [62, 63]

GDM-affected pregnant women had higher glucose levels and lower levels of various amino acids, creatinine, and glycerophosphocholine. [64]

Changes in glucose, amino acids, glutathione, fatty acids, sphingolipids, and bile acid metabolites in the amniotic fluid of GDM babies compared to non-GDM foetuses were also documented in mid-gestation in the amniotic fluid of GDM foetuses. [65]

Maternal diabetes is also related with particular structural placental alterations such as increased placental weight, increased angiogenesis (chorangiosis), and delayed villous maturation. [66]

The placenta releases or secretes glucose, proteins, and lipoproteins into the umbilical cord plasma. Some of these compounds aid in embryonic development and growth. [67, 68]

As a result, increased maternal-fetal glucose, amino acid, and fatty acid transfer might result in foetal macrosomia.

3.3) Insulin and Fetal Growth

Insulin, being an anabolic hormone, has a role in foetal growth control. [9, 98]

Fetal hyperglycemia and hyperinsulinemia are caused by maternal hyperglycemia, which increases foetal mitogenic and anabolic pathways in developing muscles, connective tissues, and adipose tissue. [99]

Overgrowth is caused by foetal hyperinsulinemia, whereas intrauterine growth retardation is caused by foetal insulin insufficiency (IUGR). [100,101]

The amniotic fluid of foetuses born to women with PGDM or GDM had high insulin levels. [35, 72, 73]

Carpenter et al. found a link between high amniotic fluid insulin levels in the second trimester and foetal macrosomia in 247 hyperglycemic pregnant women. [75]

As a result, maternal glucose intolerance during pregnancy may have an impact on foetal insulin production as early as the second trimester. Indeed, diabetes women's foetuses exhibit prominent B-cell mass within the pancreatic islets in the second trimester, compared to nondiabetic women's foetuses, and release more insulin following acute glucose exposure. With increasing gestational age, the difference in pancreatic B-cell mass between diabetic and nondiabetic foetuses becomes more evident. [102]

The insulin-secretory activity of pancreatic -cells is reflected in plasma C-peptide, which might be employed as a measure of foetal hyperinsulinemia.

Total insulin, C-peptide, and free insulin levels in umbilical vein plasma have all been found to be elevated in diabetes pregnancies. Two months after delivery, DubÉ et al. discovered a link between cord blood C-peptide levels and maternal insulin, C-peptide, and insulin sensitivity index values. [74] C-peptide levels in cord blood were evaluated in 18 pregnant women with GDM and 23 pregnant women with normal glucose tolerance (NGT). When GDM moms' kids were compared to nondiabetic mothers' offspring, higher levels of cord blood glucose were found. In general, maternal insulin, fasting C-peptide, insulin sensitivity, interleukin-6, body mass index, and newborn weight were all linked with cord blood C-peptide levels in both groups.

3.2.2) Glucose and Fetal Growth

Excessive maternal to foetal glucose transfer via abnormal function and expression of glucose transporter proteins (Glut proteins) in the placenta may cause foetal macrosomia [104]. Glucose levels were shown to be higher in foetal amniotic fluid samples from GDM moms [64,65]. The enhanced expression of GLUT-1, GLUT-4, and GLUT-9 in the term human placenta of both GDM and PGDM women associated with foetal birth weight, suggesting the significance of GLUT proteins in the stimulation of intrauterine foetal growth [105].

During the second and third trimesters of pregnancy, a longitudinal ultrasonography investigation of intrauterine development was undertaken on 37 foetuses of diabetes mothers and 29 foetuses of non-diabetic, non-smoking mothers [106]. Fetal macrosomia in GDM moms might be controlled with a sufficient daily carbohydrate intake (250 g) and a reduction in fat consumption [107]. Interestingly, term infants' weight was enhanced by 200 g in non-diabetic expectant mothers with glucose levels over 130 mg%, but maternal hypoglycemia was linked to lower birth weight [70]. These studies showed that hyperglycemia increases foetal weight, emphasising the significance of maintaining adequate glycemic control throughout pregnancy.

From 13 to 36 weeks of pregnancy, Combs et al. examined the effects of fasting and postprandial glucose levels on neonatal weight in a group of 111 women with T1DM and controls [71]. Macrosomia was linked to increased postprandial glucose levels during late gestation in 32 newborns (29 percent). Low postprandial glucose levels (less than 130 mg/dL) were linked to an increased risk of small for gestational age (SGA) babies (18 percent). To prevent the danger of foetal macrosomia, the authors recommended achieving ideal 130 mg/dL (7 mM) 1-h postprandial glucose levels [71]. In 14 closely glucose managed T1DM pregnant women, Parfitt et al. characterised the relationship between high postprandial glucose and HbA1 levels and foetal development and newborn size [108].

In a cohort of 107 women with GDM, 118 women with poor glucose tolerance, and 2020 women with normal glucose tolerance, Li et al. investigated the relationship between GDM and glucose tolerance and foetal growth [109]. Beginning in week 23, glucose levels were positively related with greater estimated foetal weight, reaching significance at week 27. Measures to minimise foetal overgrowth associated with GDM should begin at weeks 24–28, according to the authors [109]. In many countries, this gestational period is now the preferred stage for GDM screening.

Chiefari et al. discovered that foetal bio-metric growth centiles were considerably greater in women with GDM than in women with normal blood glucose tolerance, adding to the evidence for early-onset foetal overgrowth in connection to GDM [110].

Furthermore, neonates delivered to moms with early GDM diagnoses (weeks 16–18) had lower birthweight centiles than neonates born to women with late GDM diagnoses (weeks 24–28) [110].

In a population-based, retrospective cohort study of 769 pregnant women stratified into three groups based on the risk factors for developing GDM in the late second trimester, Quaresima et al. estimated the significance of screening for GDM at 16–18 and 24–28 weeks of gestation to prevent foetal macrosomia [111]. During the first trimester of pregnancy, abdominal circumference and estimated foetal weight in high-risk (HR) women with obesity, history of GDM, or indications of glucose intolerance were compared to medium-risk (MR) and low-risk (LR) pregnant women and their children. In comparison to normal glucose-tolerant women, foetal fat deposition and growth rates were considerably greater in MR and LR women with GDM. However, there was no discernible variation in their infants' weight percentiles. GDM diagnosis and therapy during 24–28 weeks of pregnancy in women with medium and low risk of foetal macrosomia were found to be adequate to avoid foetal macrosomia [111]. In comparison to normal glucose-tolerant women or MR and LR women with GDM, children delivered to HR women diagnosed with GDM at 24–28 weeks of pregnancy have a greater abdominal circumference estimated foetal weight and a higher birthweight [111]. These findings emphasise the need of detecting glucose intolerance in pregnant women early on, especially in the first trimester.

Silva et al. investigated the relationship between an infant's birthweight and the kind of diabetes therapy utilised in 705 pregnancies complicated by GDM [112]. Diet helped to correct maternal hyperglycemia, and in situations where glucose levels remained elevated, metformin and even insulin were given. Metformin therapy in GDM women reduced the incidence of SGA and was linked to babies who were appropriate for gestational age (AGA). Insulin therapy was linked to a lower risk of preterm birth, but metformin therapy paired with insulin was linked to large for gestational age (LGA) newborns [112].

In 221 women with T1DM and 87 women with T2DM, Ladfors et al. studied the role of obesity and gestational weight gain (GWG) in newborn macrosomia [113]. LGA was found in 50 percent of women with T1DM, but only 23 percent of women with T2DM. The overgrowth of the newborn was highly associated with gestational weight increase in both T1DM and T2DM women, but not with BMI. In addition, maternal HbA1c levels were revealed to be a risk factor for LGA newborns in women with T1DM but not in mothers with T2DM, particularly in the third trimester [113]. Other chemicals, in addition to high glucose, appear to penetrate the placenta and contribute to foetal overgrowth [114]. High blood levels of amino acids in the mother were also linked to foetal macrosomia [115]. As a result, diabetic mothers should use GWG with caution to avoid foetal overgrowth or other postnatal issues [116,117,118,119,120].

3.2.3) Blood Leptin Levels and Fetal Growth

Leptin is a satiety hormone released largely by adipocytes [121]. It is a 167-amino-acid product of the human leptin gene. The placental trophoblastic cells produce the majority of leptin throughout pregnancy [122,123]. It's still unknown what impact leptin plays in foetal development in the presence of maternal diabetes. Various investigations have come to differing findings and had contradicting outcomes. In gestational diabetes mothers, Atègbo et al. found higher levels of leptin in maternal circulation than in pregnant control women, but leptin levels in macrosomic kids were lower than in age-matched control newborns [76]. Maternal insulin, fasting glucose, and triglycerides were all linked to maternal blood leptin levels. In a study comparing 86 women with GDM to 48 controls, Horosz et al. found no change in maternal plasma leptin levels during later gestation [79]. According to Wolf et al., maternal insulin and leptin levels were greater than those seen in foetal circulation. LGA babies and foetal insulin were linked to foetal leptin levels, but not maternal levels [77].

In the cord blood of macrosomic newborns, higher amounts of leptin C peptide and insulin were detected compared to controls [80,81,124], and these levels were independent of maternal levels [78]. In newborn infants of PGDM mothers, blood cord leptin levels were elevated, but they returned to normal by the third day of life [82]. Chaoimh et al. discovered a link between cord blood leptin levels at birth and fat mass index in term babies [83]. However, because the data are conflicting, it's possible that the newborns' adiposity has nothing to do with leptin. Children with congenital leptin gene mutations or leptin receptor gene mutations have a normal birth weight [125,126]. It may be inferred that leptin levels are higher in macrosomic foetuses, but the mechanism by which they interact with foetal growth has yet to be discovered.

3.2.4) Blood Adiponectin Level and Fetal Growth

Adiponectin is a 30 kDa protein with 244 amino acids that is mostly produced by adipocytes but also present in other tissues, notably the placenta [127]. Adiponectin levels are negatively connected to leptin levels in the blood and are lower in obese persons [84]. It increases insulin sensitivity, glucose and lipid metabolism, as well as having anti-inflammatory properties [128]. In general, adiponectin levels in maternal blood during late pregnancy are lower in PGDM and GDM women than in non-GDM women [85], and this is linked to elevated insulin and C-peptide levels. In compared to controls, PGDM women' foetal cord blood adiponectin levels steadily rose with gestational age, according to Lindsay et al. [85]. Other researchers, on the other hand, found no link between GDM and cord blood adiponectin levels [129,130,131]. Fetal adiponectin is thought to be expressed, secreted, and circulated independently of maternal

adiponectin. As a result, it's still unclear if adiponectin plays a function in foetal growth.

3.2.5) Blood Levels of Ghrelin and Fetal Growth

The preproghrelin gene Ghrl encodes a 28-amino-acid peptide that is predominantly produced by entero-endocrine cells of the gastrointestinal system and the hypothalamus [132,133]. Ghrelin levels in maternal circulation are reduced throughout pregnancy [134,135], most likely as a result of adaptive mechanisms expressed by insulin resistance and pituitary GH replacement by placental GH [55].

GDM women had higher levels of ghrelin expression in their term placentas than non-diabetic mothers [86,87]. The levels of foetal ghrelin were shown to be negatively related to neonatal birthweight [88]. Ghrelin levels in the umbilical cord were found to be inversely associated to birth weight z- score (adiposity) and cord blood glucose by Farquar et al. [89]. They also found a positive relationship between foetal ghrelin plasma levels and gestational age in AGA and LGA newborns, but a negative relationship in SGA infants [89]. In compared to 40 children born to non-diabetic moms and 42 infants born to women with GDM treated just by a low-energy diet, Ng et al. found lower foetal ghrelin levels in 38 newborns of mothers with type 1 PGDM treated with insulin. Hehir et al. found no significant change in maternal plasma or foetal umbilical vein plasma ghrelin levels at 36 weeks gestation in a cohort of ten mothers with PGDM and ten controls in a prospective trial [87]. The precise function of ghrelin activity in foetal growth is yet unknown.

3.2.6. Human Placental Growth Hormone (PGH)-IGF Axis and Fetal Growth

PGH is produced by placental syncytiotrophoblastic cells, and it enters the maternal blood during the sixth week of pregnancy, progressively replacing pituitary growth hormone [54]. PGH affects foetal development by increasing food availability, boosting gluconeogenesis, lipolysis, and anabolism in maternal tissues, or by regulating IGF-I [55,136]. In pregnancies complicated by intrauterine growth retardation (IUGR), the levels of total PGH and IGF-I in maternal circulation decrease in the third trimester [91]. IGF-1 levels in the womb are linked to neonatal adiposity and may aid fat formation in the newborn [92].

In pregnancies with type 1 PGDM, maternal PGH was found to be substantially linked with foetal weight measured by ultrasonography, birth weight, and birth weight centile in a prospective study by Higgins et al. [93]. In diabetes and non-diabetic pregnant women, however, PGH levels in maternal and foetal circulations were similar, and foetal PGH levels did not correlate with foetal growth [93]. Ringholm et al. discovered lower levels of maternal PGH in women with large for gestational age babies (LGA) during early pregnancy complicated by type 1 PGDM, but the levels of maternal PGH were not linked with insulin in these women [94]. PGH may play a modulatory function in foetal development via fetoplacental feedback, according to McIntyre et al. [137].

PGH is a modulator of maternal insulin-like growth factor-I (IGF-I), an IGF family member that promotes both mitogenic and anabolic pathways [55]. The interaction of IGFs with certain IGF-binding proteins was essential for their bioavailability (IGFBPs). Several researches looked at the relationship between IGF-I and IGFBPs in maternal plasma in DM-affected pregnancies. Maternal IGF-I levels were lower in diabetes pregnancies [95], while foetal IGF1 serum levels were higher in diabetic newborns compared to non-diabetic controls [96]. In T1DM pregnancies, higher levels of IGFBP3 were seen in both maternal and foetal serum compared to non-diabetic controls, owing to enhanced proteolysis in maternal but not foetal serum [93].

McIntyre et al. looked studied the amounts of growth hormone binding protein (GHBP) in maternal circulation in 140 women with T1DM, T2DM, or normal glucose tolerance [91]. GHBPs levels in the maternal circulation of non-diabetic women decreased gradually throughout pregnancy and were significantly linked with maternal weight and BMI [91]. In the blood of T2DM pregnant mothers whose kids were SGA, however, higher amounts of GHBPs were found. As a result, a drop in GHBPs in the maternal circulation may have an impact on foetal development and mother glycemic status.

At the start of mid-gestation, SGA children have higher amounts of IGF binding protein 1 (IGFBP1) in their amniotic fluid [138]. IGFBP3 levels in the amniotic fluid are linked to birth weight in LGA newborns [97].

It may be inferred that numerous growth hormones, such as glucose, insulin, PGH and IGF-I, and IGFBP, have a role in foetal growth and development. The IGF1–IGF2 axis may be dysregulated, especially in diabetes pregnancies that are unmanaged [106]. The precise involvement of each of these variables in foetal growth interference is yet unknown.

Insulin resistance is mediated by pregnancy-related hormones such as oestrogen, progesterone, cortisol, and cytokines, as well as additional placental growth hormones such as hPGH and placental lactogen that enter the maternal blood. Adipocytokines, such as leptin, adiponectin, and tumour necrosis factor-(TNF-), are also produced by adipose tissue and may contribute to insulin resistance. Insulin resistance causes glucose intolerance, which leads to hyperglycemia. This leads to placental alterations as well as an excess of glucose, amino acids, and lipids in the foetus. Hyperinsulinemia is produced by the foetus in response to maternal hyperglycemia, which lowers foetal blood glucose levels while also increasing foetal fat tissue and enhancing development. Furthermore, PGH promotes foetal gluconeogenesis and lipogenesis, resulting in increased foetal growth.

3.3. Low Birth Weight in Infants of Diabetic Mothers (LBW, SGA)

The number of low-birth-weight babies (SGA) born to PGDM moms decreased once insulin was introduced. Low birth weight babies are associated with severe diabetes vascular problems, hypertension, or renal illness in the mother [139,140,141,142]. Diabetes medication that is excessively strict might result in hypoglycemia, which can contribute to low birth weight [112]. Langer et al. looked at the link between good glycemic management and good perinatal outcomes in women with GDM [143]. They discovered that women with GDM who had mean gestational blood glucose levels below 87 mg/dL had a greater incidence of SGA newborns (20%) than women without GDM who had only 11% of SGA infants. SGA, like macrosomia, is linked to a number of illnesses, including hypertension, heart disease and diabetes [143,144,145,146,147].

3.4. Follow-Up Studies of Weight and Height in Children of Diabetic Mothers

Many prenatal and postnatal variables, particularly those that are predominantly linked with nutrition throughout early life, impact the growth and development of the kids of diabetes mothers.

Insulin resistance, obesity, cardiovascular disease, and type 2 diabetes mellitus have all been linked to reduced foetal development [148,149]. Macrosomia, or foetal enlargement, is linked to severe neonatal and postnatal morbidity. In addition, aberrant weight growth in childhood and adolescence is associated with dysregulation of the GH–IGF axis, adrenal, and gonadal function [150]. Barker et al. found that infants who were underweight at birth were more likely to be overweight during childhood and adolescence, and that they were more likely to have coronary heart disease later in life [151]. GDM is linked to childhood obesity and a different development pattern in LGA newborns born to non-diabetic mothers than in AGA infants [152].

3.4.1. Postnatal Growth of Low Birth Weight (SGA) Infants

Under proper dietary and care settings, small-for-gestational-age (SGA; birthweight 10th centile) newborns show rapid compensatory postnatal growth, or "catch-up growth," notably in the first year of life, to attain the genetically predicted size at maturity [153,154]. This enhanced compensatory development is thought to be caused by neuroendocrine system adaptations, or by faster cell proliferation in skeletal growth plates and non-skeletal tissues, or both [155,156]. Fast catch-up growth to about the 30th percentile in the first few months, followed by slow catch-up growth around the 50th percentile by 7 years, was proposed as the best development pattern for term SGA newborns, reducing the likelihood of problems in adulthood [157].

There are just a few research on SGA children born to diabetes moms' postnatal development. Boghossian et al. looked at the growth of a group of 10,781 extremely preterm SGA children delivered to diabetes moms at 22–28 weeks gestation [158]. Women were given insulin before becoming pregnant, started insulin therapy during pregnancy, or were not given insulin at all. Extremely preterm SGA children of mothers treated with insulin before pregnancy had lower weight, length, and head circumference z scores than moms with T2DM who were not treated with insulin at 18–22 months of age [158].

The postnatal growth of 10 children of women with PGDM complicated by nephropathy and 30 offspring of mothers with PGDM without nephropathy was compared by Biesenbach et al. [139]. On follow-up to three years of age, children born to PGDM moms with nephropathy showed persistently decreased development, with almost half of the ten children having body weight and height below the 50th percentile. Children born to PGDM women who did not have nephropathy had weight and height that were above the 50th percentile [139].

3.4.2. Postnatal Growth of Appropriate for Gestational Age (AGA) or Macrosomic Infants

As teens and adults, LGA newborns are more likely to be overweight and taller [159,160,161]. Silverman et al. discovered in a follow-up research that the increased birth weight observed in over 50% of children delivered to moms with GDM and PGDM normalised after one year [35]. By the age of five, the children had gained a substantial amount of weight, and by the age of eight, more than half of the children were overweight in the 90th percentile or above, with a significantly greater height. Rizzo et al. observed similar effects in their investigations on diabetes mothers' children [159], as did Vohr and McGarvey, who discovered that LGA babies of moms with GDM have higher fatness at one year of age [161]. Tarry-Adkins et al. conducted a comprehensive review and meta-analysis of newborns of GDM mothers who were treated with metformin rather than insulin to regulate glucose levels [162]. At delivery, babies whose mothers were given metformin weighed 108 grammes less than those whose mothers were given insulin. Children born to metformin-treated mothers were 0.44 kg heavier at 18–24 months and had a higher BMI (by 0.8 kg/m2) at 5–9 years of age than children born to insulin-treated mothers [162].

Ornoy and colleagues compared the weight and height of 57, 6–12-year-old children born to women with well-controlled PGDM and 32 similar-aged children born to moms with GDM to control children of comparable ages. The majority of the infants were born at a healthy weight [8,163,164]. Children of diabetes moms weighed more and stood taller than age and socioeconomic status (SES) matched control children, especially when they were 9–12 years old. There was no link between birth weight and post-examination weight. In terms of head circumference, there was no significant difference between the offspring of diabetes moms and the controls. It may be established that children born to diabetes moms are heavier and taller than children born to non-diabetic mothers. Controlling maternal weight before to pregnancy, weight growth

throughout pregnancy, and precise diabetes control can all help to prevent macrosomia in diabetics [165,166].

4. The Effects of Diabetes in Pregnancy on the Newborn Infant and in the Neonatal Period

Both PGDM and GDM are linked to considerable morbidity in children, which can be reduced with proper diabetes management before and throughout pregnancy [167]. A recent large retrospective cohort study from the United States found that neonates born to mothers with PGDM had a 2.27 (95 percent CI 1.952.64) times higher risk of composite severe neonatal morbidity, including respiratory distress syndrome and mechanical ventilation, than those born to mothers without diabetes or to mothers with GDM (aOR 1.96, 95 percent CI 1.632.35). They did not, however, detect any link between maternal diabetes and newborn mortality, despite previous research [167] finding such a link.

4.1. Postnatal Complications

4.1.1. Diabetes Associated Stillbirth and Perinatal Death

The link between diabetes pregnancy and stillbirth is well-established. Antepartum stillbirth is defined as the death of a foetus before the commencement of labour, which happens at or after 20 weeks of pregnancy or with a birth weight of more than 350 grammes. In a study of the literature, Smith et al. discovered that diabetes was the medical condition most significantly linked to stillbirth [168]. Diet-treated diabetes had an odds ratio of 1.7–2.2, whereas insulin-treated diabetes had an odds ratio of 1.7–7.7. Both normal and deformed foetuses were shown to have an elevated risk [168]. Stillbirth rates in type 1 and type 2 diabetes were 4.0 and 5.1 times higher than in the non-diabetic population ($p < 0.001$), according to the Scottish Morbidity Record of PGDM [169]. Uncontrolled hyperglycemia, obesity, past caesarean delivery, congenital birth abnormalities, and foetal development limitation were all risk factors for stillbirth in diabetic mothers [170]. In a meta-analysis of 70 trials, Syed et al. found that excellent diabetes diagnosis and management resulted in a 10% reduction in stillbirths [171]. When comparing 712 singleton antepartum stillbirths to 174,097 singleton live births, Reddy et al. discovered that preexisting diabetes had a hazard ratio of 2.7 when compared to normal pregnancies [172].

Bradley et al. used cordocentesis to gather foetal blood samples from women with type 1 diabetes between 20 and 40 weeks gestation in order to better understand the aetiology of stillbirth in diabetic pregnancies. In the third trimester, they discovered severe acidosis ($p < 0.001$) and hyper-lacticaemia ($p < 0.01$). There were substantial relationships between plasma lactate and PO2, but not with birth weight [173].

In the Scottish Morbidity Record [169], perinatal mortality (defined as a child delivered after 24 weeks' gestation who did not breathe or exhibit signs of life, or died in the first week of life) was 3.1 times more prevalent in type 1 diabetes pregnancies and 4.2 times more common in type 2 diabetes pregnancies. Compared to controls (5,523,305 women), Chinese women with impaired fasting glucose (847,737 women) and diabetes (76,297 women) had a higher rate of perinatal death (OR 1.08; 1.03–1.12; $p < 0.001$) [174]. Chen et al. found that in the Canadian population, first Nations people had a considerably greater risk of perinatal mortality from PGDM than non-Indigenous people (5.1-fold compared to 1.8-fold). They hypothesised that poor glycemic control, which was more frequent among First Nations women, may account for some of the discrepancy [175].

4.1.2. Time of Delivery

Because poor glycemic management increases the risk of mortality throughout pregnancy, the time of delivery is critical for avoiding stillbirth and neonatal death. According to the American College of Obstetricians and Gynecologists (ACOG), the recommended gestational age for delivery varies depending on the type of diabetes and the degree of control. PGDM with vascular complications, poor glucose control, or prior stillbirth: 36 + 0–38 + 6 weeks; PGDM with vascular complications, poor glucose control, or prior stillbirth: 36 + 0–38 + 6 weeks; PGDM with vascular complications, poor glucose control, or prior stillbirth: 36 + 0–38 + 6 weeks; PGDM with vascular complications, poor glucose control, For GDM, nutrition and exercise must be well-controlled. 39 + 0–40 + 6 weeks; well managed on meds 39 + 0–39 + 6 weeks; late preterm/early term, personalised [176]. Because there is insufficient evidence that the advantages of lowering shoulder dystocia risk exceed the risks of early delivery, suspected foetal macrosomia is not a reason for induction of labour before 39 + 0 weeks of pregnancy [43].

Harper et al. compared perinatal outcomes of scheduled births at 37, 38, 39, and 40 weeks to expectant management to enhance pregnancy outcomes and reduce perinatal mortality. The risk of perinatal mortality was low (3/1000 births) in 4905 diabetic pregnancies—of whom 1012 were insulin-dependent—at any gestational age investigated, including individuals who were insulin-dependent and had a risk of 6/1000 births or less [177]. A composite unfavourable neonatal outcome of assisted ventilation >30 minutes, birth damage, seizures, or a 5-min Apgar score of ≤ 3 had a < 2% chance of occurring. They came to the conclusion that, because diabetes pregnancy is linked to a higher likelihood of stillbirth, early delivery may be a viable choice for these pregnancies [177].

4.1.3. Mode of Delivery

The estimated foetal weight influences the route of delivery in diabetes pregnancy (EFW). The American College of Obstetricians and Gynecologists suggests using ultrasound or clinical assessment to determine birth weight. In diabetic pregnancies with an EFW exceeding 4500 gr on ultrasound (US), a caesarean section is advised [43].

Even among pregnancies with lower EFW, the widespread use of ultrasound to assess foetal weight increased the likelihood of CS. Even after accounting for birth weight, Dude et al. discovered a higher risk of CS among women who had US EFW 5 weeks before to delivery [178]. 231 of the 304 diabetic pregnancies had US EFW, with 66 (28.6%) having a pre-delivery diagnosis of LGA. Only 23 (34.9 percent) of this cohort were LGA after birth. Six (3.6 percent) of the 165 women diagnosed with EFW AGA before to birth were LGA. Pregnancies with an LGA baby were more likely to have a CS if the baby was diagnosed with an arrest condition [178].

There is no standard of treatment for diabetic mothers with retinopathy during birth. Vitreous haemorrhage is more likely in women with PGDM and proliferative retinopathy. Due to the Valsalva manoeuvre, Ab-delaal et al. hypothesised that vaginal birth would be dangerous in women with severe, non-proliferative, or proliferative diabetic retinopathy, and proposed that a C section might reduce the risk of vitreous haemorrhage during vaginal delivery [179].

4.1.4. Shoulder Dystocia

Macrosomia is linked to severe delivery-related complications, including shoulder dystocia. The EFW showed no clinically meaningful impact in predicting shoulder dystocia in a meta-analysis of 41 trials that included 112,034 individuals who received third-trimester ultrasounds for the prediction of macrosomia. The majority of investigations found sensitivities of less than 30%, with only one small research reporting a sensitivity of more than 50% [180]. An increased rate of shoulder dystocia was linked to untreated hyperglycemia throughout pregnancy (risk ratio, 1.25 compared to controls). Even when greater glucose levels were indicated, treated diabetes in pregnancy had a shoulder dystocia rate equivalent to controls [181]. 149 women who received pre-pregnancy treatment had no children with shoulder dystocia, compared to 6/265 women who did not get pre-pregnancy care (p = 0.07) [182]. Kekalainen hypothesised that women with type 1 diabetes would benefit from pregnancy planning. Women who had planned pregnancies had lower HbA1c levels and fewer congenital abnormalities; however, there was no change in the rate of shoulder dystocia, which was 3/96 in planned against 3/49 in unplanned pregnancies [183].

4.1.5. Prematurity and Prematurity Complications

Multiple pregnancies, increased urinary tract infections, poor glucose control, preeclampsia, and poor foetal development are all linked to an increased likelihood of preterm in diabetes pregnancies. Berger et al. looked at 30,139 pregnancies that were preterm, and 7375 of them had diabetes or diabetes aggravated by hypertension or obesity. Diabetes had a relative risk of 3.51, 95 percent confidence interval 3.26–3.78, diabetes complicated by hypertension had a related risk of 6.34, 95 percent confidence interval 5.14–7.80, and diabetes complicated by obesity had a relative risk of 3.09, 95 percent confidence interval 2.80–3.40 [184].

Women with diabetes who also had hypertension and obesity had the greatest risk—11.26, 95 percent CI 9.40–13.49 [184]. Riskin et al. studied 526 diabetic pregnancies and found that preterm was more prevalent in PGDM (31.9%) than GDM (11.3%) and only 4.9 percent in controls (p = 0.001) [185].

Soliman et al. also discovered that premature birth was considerably greater in women with PGDM and GDM (13.7 percent and 9%, respectively) compared to controls (6.4 percent; p 0.001) among 3027 women with GDM and 233 women with PGDM. [186]. Antoniou et al. discovered 8.2% preterm births among 576 diabetic pregnancies with HbA1c less than 5.5 percent at the end of pregnancy [187]. Prematurity was found to be more prevalent in women with type 1 and 2 PGDM who did not get pre-pregnancy care (17.7% of 265) than in women who did receive pre-pregnancy treatment (11.4 percent of 149), p = 0.09 [180]. Kawakita looked at 222,978 singleton births, of which 11,327 (5%) had GDM and 3296 (1.5%) had PGDM, and found a preterm rate of 16.3 percent and 32.3 percent, respectively, in GDM and PGDM, compared to 10.9 percent in controls [188].

4.1.6. Course at the Neonatal Intensive Care Unit (NICU)

Premature children delivered to diabetes moms have a more difficult time in the NICU, owing to respiratory morbidity, according to most research. Compared to controls, Battarbee et al. looked at the outcomes of 2993 children born to women with PGDM and 10,549 infants delivered to mothers with GDM [167]. The median gestational age at delivery for neonates delivered to mothers with PGDM was one week sooner than those born to women with GDM, and nearly two weeks earlier than controls (39.1 weeks). They found that respiratory morbidity led to more intensive care unit admissions (OR 4.89 and 1.68, respectively) (see below). They found no link between maternal diabetes and infant necrotizing enterocolitis, intraventricular haemorrhage of grade 3 or 4, or mortality [167]. Hitaka et al. analyzed very low birth weight (VLBW) (1500 gr) newborns in Japan and found no significant differences in mortality and morbidity between children born to mothers with or without hyperglycinemia during pregnancy [189]. Only infants born between 2003 and 2010 had a greater rate of respiratory distress syndrome (RDS) than controls, not those born between 2011 and 2013. The definition of hyperglycemia was revised in 2010, resulting in a fourfold rise in the number of GDM pregnancies to 6–12%. The elevated risk of RDS shown exclusively in children born to women who had hyperglycemia during pregnancy before the GDM diagnostic criteria were relaxed reflects the degree of maternal hyperglycemia at the time [189]. Grandi et al. looked at the outcomes of diabetes mothers' VLBW babies (both GDM and PGDM) from the NEOCOSUR South American Network (Argentina,

Brazil, Chile, Paraguay, Peru, and Uruguay) [190]. From 2001 to 2010, there were 304 VLBW pregnancies out of 12,146 total. NEC grades 2–3 were the only condition that was independently related with the diabetes group of women after the logistic regression analyses were adjusted (OR 1.65). Mechanical ventilation, PDA, late-onset sepsis, and the combined major complications index (death or BPD/IVH grade 3–4/NEC 2–3) (OR 1.08, 1.17, 0.45, and 1.01, respectively [190]) showed no significant differences. Boghossian et al. studied the outcomes of extremely preterm infants (22 to 28 weeks gestation) born to women who used insulin before pregnancy, insulin only during pregnancy, and controls at a Neonatal Research Network centre run by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (2006–2011) [158]. When compared to controls, infants of mothers who were given insulin before pregnancy had a higher incidence of NEC (RR 1.55) and late-onset sepsis (RR1.26). ROP was more prevalent in the pre-pregnancy insulin group (RR = 1.23), compared to those who took insulin solely during pregnancy. There were no significant changes in the risk of PDA, early-onset sepsis (EOS), IVH, PVL, or bronchopulmonary dysplasia among the three groups (diabetics and controls) (BPD). In comparison to individuals who started insulin during pregnancy and controls, infants of moms who started insulin before pregnancy had a reduced average head circumference at term. There were no significant variations in the individual components of the neurodevelopment index between the three groups at 18 to 22 months [158]. Persson et al. looked at the morbidity of diabetes mothers' VLBW babies [142]. Of the 76,360 extremely preterm, singleton children delivered between 2007 and 2015 at 24 to 31 weeks gestation with birth weights of less than 1500 g across seven national networks (Canada, Finland, Israel, Italy, Japan, Sweden, and the United Kingdom), 3280 (4.3 percent) were born to diabetes mothers. RDS, IVH grade 3–4 or cystic PVL, treated PDA, severe ROP, BPD, and NEC risk estimations were comparable in diabetes and non-diabetic pregnancies (OR 1.05, 0.91, 1.01, 1.01, 1.01, 0.94, and 1.1, respectively). Most gestational ages, all sexes, and all country groups studied yielded similar results [142]. Despite the aforementioned findings, several research have linked maternal hyperglycemia to a higher prevalence of ROP. The incidence of ROP related with maternal diabetes was 2.64 (p 0.01) among newborns weighing less than 1500 g, according to Opara et al. [191]. They postulated that ROP and diabetic retinopathy share pathogenic processes since both are retinal vascular disorders characterised by leakage and/or neovascularization from damaged retinal vessels [191]. Tunay et al. also discovered that maternal diabetes increased the risk of ROP in preterm newborns weighing more than 1500 grammes, finding a 25-fold and 6-fold increase in the risk of ROP and Type 1 ROP, respectively, independent of the type of maternal diabetes [192].

4.1.7. Respiratory Morbidity

At all gestational ages, diabetic pregnancy is linked to an increased risk of newborn respiratory illness. Hyperglycemia and hyperinsulinemia in the womb have been proposed as possible causes of delayed lung maturation. In 621 diabetic pregnancies (261 with excellent glycemic control, 360 with poor glycemic control), delayed development of phosphatidyl-glycerol, a marker of lung maturity, was linked to poor glycemic control [193]. The relationship between inadequate glycemic management during pregnancy and an increased risk of respiratory morbidity has been studied using a variety of animal models. McGillick et al. investigated the effect of intra-fetal glucose infusion on the mRNA expression of glucose transporters, insulin-like growth factor signalling, glucocorticoid regulatory genes, and surfactant in the lung of late-gestation sheep foetuses and found that, despite an unchanged number of surfactant positive pneumocytes type B, surfactant protein mRNA expression was reduced in the lung after glucose infusion [194]. Insulin reduced surfactant protein a gene transcription in human lung epithelial cells, according to Miakotina et al. [195]. The higher prevalence of RDS in diabetic pregnancies may be due to a delay in surfactant system development following a large rise in foetal plasma glucose and insulin concentrations. In a study of 222,978 singleton pregnancies, Kawakita et al. found that 11,327 had GDM and 3296 had PGDM [188]. Neonatal respiratory morbidity was shown to be considerably greater in all age groups, and in PGDM compared to GDM, as well as both compared to controls. They concluded that diabetes is a risk factor because the infant respiratory morbidity associated with diabetes was not entirely explained by prematurity-related physiologic immaturity [188]. Battarbee et al. looked examined neonates born between 24 and 41 weeks of pregnancy in two large multisite US cohorts, the Cesarean Registry and the Consortium on Safe Labor [167]. When 2993 newborns of PGDM mothers and 10,549 infants of GDM mothers were compared to 196,006 controls, RDS (OR 3.09 and 1.23, respectively) and mechanical ventilation (OR 2.63 and 1.14, respectively) were shown to be linked with PGDM and GDM [167].

4.1.8. Hypertrophic Cardiomyopathy

Diabetic moms' foetuses and neonates have been shown to have myocardial hypertrophy. However, because it is asymptomatic in the majority of instances, its actual occurrence in infants of diabetes moms is unknown. Hyperinsulinemia and hypoxia have an impact on the foetal heart. In the third trimester, foetuses of both PGDM and GDM pregnancies exhibited increased intraventricular septal thickness compared to controls, according to a meta-analysis of 39 studies [196]. According to a study of the literature, asymptomatic and symptomatic neonates had an incidence ranging from 13 percent to 44 percent [197]. El-Ganzoury et al. discovered a link between interventricular septal

thickness and poor maternal glycemic management (HbA1c 7%) [198]. Topcuoglu et al. compared 41 diabetic mothers' children to 51 controls to better understand the pathophysiology of cardiomyopathy in diabetes pregnancy [199]. In the first three days, echocardiographic and Doppler ultrasound scanning revealed that the IDM group had significantly higher inter-ventricular septal thickness at diastole, posterior wall thickness (p = 0.002), posterior wall thickness in diastole, and left ventricular mass (p = 0.02, 0.002, 0.03 and 0.04 respectively). The oxidative stress indicators were correlated with HbA1c, interventricular septum in systole and diastole, and left ventricular mass [199].

Functional echocardiography has been utilised to examine foetuses and neonates who have hemodynamic alterations owing to extra-cardiac disorders in recent years. Using functional echocardiography and spectral Doppler, Peixoto et al. examined the influence of PGD type 1 (31 pregnancies) and type 2 diabetes (28 pregnancies) on foetal cardiac function to controls (120 pregnancies) [200]. Fetuses were measured at 30.2, 29.7, and 31.1 weeks of pregnancy. The left ventricular myocardial performance index (p 0.001) was found to have a significant relationship with adverse neonatal outcomes (at least one of: foetal death, neonatal death, Apgar score 7 at the 5th minute, admission to the intensive care unit, macrosomia, respiratory distress, hyperglobulinemia, hyperbilirubinemia, hypocalcemia, sepsis, and hypoglycemia) [200]. Between 21 well-controlled term diabetes pregnancies and 54 normal pregnancies, Patey et al. examined foetal and neonatal cardiac geometry, myocardial deformation, and left ventricular torsion [201]. Seven of the 21 women with diabetes had insulin-controlled PGDM, and 14 had metformin-treated GDM. The heart geometry, myocardial deformation, and ventricular function of diabetic women's foetuses were all significantly altered. Their left ventricle was smaller and narrower. Diabetic mothers' babies experienced lasting changes in left ventricular chamber geometry after delivery, including thicker walls, smaller and shorter ventricles, and moderate tricuspid regurgitation [201]. The heart hypertrophy is generally temporary, resolving between two weeks to six months of birth; however, the long-term effects of the prenatal and postnatal alterations are unknown. Blais et al. studied 3-year-old children's cardiac relaxation in connection to their mother's insulin resistance during pregnancy [202]. They compared the left ventricular mass of 29 infants from GDM moms, 36 children from insulin-resistant mothers (women whose fasting and post-OGTT glucose levels were within normal ranges), and 41 controls and found that it was normal and comparable in all three groups. The GDM and insulin-resistant groups were more likely than the controls to have impaired myocardial relaxation (however, the differences did not reach statistical significance). Subjects with poorer cardiac relaxation had higher median cord blood C-peptide and insulin levels, although this did not achieve statistical significance [202]. Rijpert et al. discovered that heart dimensions and systolic and diastolic function were normal at 7–8 years of age in 30 diabetic mothers' kids compared to 30 controls, including three diabetic mothers' offspring with neonatal cardiac hypertrophy [203]. Maternal glycemic management throughout pregnancy and neonatal macrosomia were not linked to a poor cardiac prognosis [203]. It may be inferred from these research that diabetic-induced cardiomyopathy in newborns is usually transitory.

4.1.9. Perinatal Asphyxia

Maternal hyperglycemia causes foetal hyperglycemia and hyperinsulinemia, as has been demonstrated numerous times. The concept that prenatal hyperglycemia increases the risk of foetal hypoxia is supported by data from both experimental and clinical research. Aside from foetal hypoxia, changes in heart shape and function (e.g., hypertrophic cardiomyopathy) and placental anomalies may further increase the risk of newborn problems in diabetes mothers' kids. Huynh et al. found that placentas from PGDM pregnancies had an increased rate of villous immaturity as well as increased volume and surface area of parenchymal tissue in a comprehensive study, whereas placentas from GDM pregnancies had largely increased weight [66].

Castelijn et al. compared the outcomes of 117 women with type 1 diabetes, 59 women with type 2 diabetes, and 303 women with gestational diabetes against 15,260 controls who gave birth between 2004 and 2014 [204]. In comparison to controls, women with type 1 and type 2 diabetes were more likely to deliver via unscheduled caesarean section. In the offspring of mothers with type 1 diabetes, the mean umbilical artery (UA) pH was lower. In type 1 diabetes, the probability of UA pH 7.20 or 7.10 was considerably higher than in the control group (OR 1.88 and 3.35 respectively). In type 1 diabetes, the frequencies of UA pH 7.20 and UA pH 7.10 were similarly higher than in gestational diabetes (OR 2.01 and 2.64, respectively). In addition, when foetal distress was the reason for an instrumental delivery, women with type 1 diabetes had greater rates of UA-pH 7.20 or 7.10 than controls. Infants born to mothers with HbA1c levels greater than 53 mmol/mol had a higher incidence of UA pH < 7.20 and UA pH < 7.10 than those born to mothers with HbA1c levels less than 42 mmol/mol . Except for preterm, type 1 and type 2 diabetes patients had a greater probability of NICU admission than controls [204]. Diabetic pregnancies were linked to a higher risk of poor neonatal adaption, according to Kawakita et al. [188]. Oxygen, bag and mask ventilation, Continuous positive airway pressure (CPAP), intubation, chest compressions, and epinephrine injection were all used more frequently. PGDM offspring had worse outcomes than GDM offspring, and both were worse than controls, p < 0.01 [188]. Cnattingius et al. compared the

outcomes of 5941 and 711 newborns of type 1 and type 2 diabetes mothers to 1,337,099 controls who were also controlled for maternal obesity [205]. When maternal factors were taken into account, the risks of a low Apgar score (0–6) at 5 minutes were higher in type 1 and type 2 diabetes patients than in controls (OR 2.62 and 1.60, respectively, and 2.67 and 1.25, respectively, when also adjusted for maternal BMI). The kids of mothers with type 1 and type 2 diabetes had similar rates of severe asphyxia-related newborn morbidity (defined as neonatal convulsions and/or hypoxic–ischemic encephalopathy) and were significantly higher than the offspring of mothers without diabetes. Maternal obesity and overweight were linked to a higher likelihood of a low Apgar score and severe asphyxia-related newborn morbidity in all three groups [205].

Website-based systems or mobile terminal devices can be used to help healthcare practitioners monitor patients' health-related indicators and give timely medical feedback and assistance to enhance patients' physical and psychological well-being. The impact of remote communication technologies in enhancing pregnancy outcome was investigated in a meta-analysis of 32 randomised controlled trials (RCTs), which included 5108 patients with GDM (2581 trained via telemedicine and 2527 controls) [206]. The majority of the research was done in China (21 studies, 65.6 percent). When compared to controls, the telemedicine group experienced substantial improvements in glycated haemoglobin (HbA1c) control [mean difference ($p < 0.01$)], fasting blood glucose control ($p < 0.01$), and 2-hour postprandial blood glucose control ($p = 0.01$). In a meta-analysis of five investigations, telemedicine treatments were shown to reduce the incidence of newborn asphyxia (RR = 0.17, $p < 0.01$) [206].

4.1.10. Neonatal Hypoglycemia

Hypoglycemia is a well-known issue in diabetic moms' babies. Hypoglycemia was more common in PGDM pregnancies than in GDM and control pregnancies (28.9%, 7.1 percent, and 1.7 percent, respectively, $p < 0.001$) [185]. Yu et al. discovered that type 1 diabetes was linked to an elevated incidence of newborn hypoglycemia (OR 26.62) in a meta-analysis of nearly 40 million pregnancies from 100 studies [207]. Pre-pregnancy treatment may have little or no effect in lowering the incidence of newborn hypoglycemia (RR 0.93) in 880 diabetic pregnancies, according to Wahabi et al. [208]. Women with Type 1 diabetes from 31 hospitals in Canada, England, Scotland, Spain, Italy, Ireland, and the United States were tested on the use of real-time continuous glucose monitoring throughout pregnancy [209]. Continuous glucose monitoring, compared to routine capillary glucose monitoring, resulted in a lower incidence of newborn hypoglycemia needing intravenous dextrose therapy (OR 0.45, $p = 0.0250$) [209]. Antoniou et al. looked at the kids of 576 women who had GDM and found that 10.7% of them had neonatal hypoglycemia. The degree of maternal illness was linked to a two-fold greater incidence of newborn hypoglycemia ($p = 0.032$) when maternal therapy was required [187].

4.1.11. Fetal Macrosomia (LGA)

In diabetes pregnancies, foetal hyperinsulinemia is the most common cause of foetal overgrowth. In a study of 280 Swedish pregnancies, 53 percent of the infants of women with PGDM were LGA, compared to just 13 percent of the children of women with GDM ($p = 0.0001$) [210]. When compared to women with GDM, women with type 1 PGDM had a 9.5 times greater chance of having LGA offspring. In multiple regression analyses, women with diabetes type 1 (OR 31.3, $p < 0.001$), multiparity (OR 6.2, $p = 0.003$), early pregnancy BMI > 30 kg/m2 (OR 7.2, $p = 0.003$), gestational weight gain ≥ 8 kg (OR 3.8, $p = 0.047$), and living alone (OR 18.4, $p = 0.02$) were significantly more likely to develop macrosomia [210]. In a meta-analysis, Wahabi et al. discovered that diabetic women's pre-pregnancy treatment had little or no influence on macrosomia rate (RR 1.06; nine studies, 2787 women) [208]. The rate of macrosomia is affected by the differing definitions of GDM (i.e., the Diabetes and Pregnancy Study Group (IADPSG) criteria against the National Institute for Health and Care Excellence (NICE) in the United Kingdom criterion). Koivunen et al. looked examined the results of 4033 women who had been tested for GDM [211]. When the IADPSG (31.0 percent) criteria were used to diagnose GDM, the proportion diagnosed was 2.4 times greater than when the NICE criteria were used (13.1 percent). Regardless of whatever diagnostic criteria were used, the incidence of Large for gestational age > 90% and Large for gestational age, > + 2 SD did not vary between treated diabetes pregnancies and controls. Mild untreated hyperglycemia was linked to greater birth weights (OR LGA >90 percent IADPSG 1.51 and NICE 1.43) and LGA > + 2 SD (IADPSG 1.17 and NICE 1.18) according to both criteria [211].

4.1.12. Fetal Growth Restriction (FGR)

Pregnant women with diabetes mellitus are more likely to develop hypertension, which can impact foetal development. The balance between the increased blood glucose supply from the mother to the foetus via a heavier placenta and foetal hyperglycemia and hyperinsulinism, as well as the decreased blood glucose supply due to placental dysfunction in women with hypertension, may determine fetal growth in pregnant women with DM and hypertension. There were 14.23% (924,034) pregnant Chinese women with pre-pregnancy fasting blood glucose abnormalities, with 1.18 percent (76,297) having PGD and 13.15 percent (847,737) having impaired fasting glucose (5.6–6.9 mmol/L) among 6,447,339 pregnant Chinese women . Women with impaired fasting glucose and diabetes had a higher risk of SGA babies than women with normal blood glucose (OR 1.06 $p = 0.007$ and 1.17 $p = 0.008$, respectively). There was a linear relationship between fasting blood glucose and SGA ($p = 0.001$). Morikawa et al. looked at 7893 women and found that 154 of them had PGDM (Type 1 DM 45 and Type

2 DM 109 women) [212]. Type 1 diabetes women had considerably greater birthweights than type 2 diabetic women ($p < 0.05$); nevertheless, the occurrence of FGR was equal in both diabetic groups. Women with type 1 diabetes had a comparable risk of FGR regardless of pregnancy hypertension, while type 2 diabetes women had a substantially greater rate of FGR when the pregnancy was complicated by hypertension ($p < 0.05$) [212]. 9.4% of the babies in a study of 576 mothers with GDM were SGA. Pre-pregnancy BMI was found to have an inverse relationship with SGA [187]. The incidence of babies with malnutrition (ponderal index (PI) 10th centile) was 8.7% in a study of 231 moms with GDM. In GDM neonates identified as SGA by tailored curves, the chance of presenting a PI 10th centile was 4.24 times greater than in newborns classified as AGA (RR 4.24) [213]. In a meta-analysis, Wahabi et al. discovered that diabetic women's pre-pregnancy treatment resulted in a significant reduction in SGA (RR 0.52; six trials, 2261 women) [208]. In the first trimester of pregnancy, pre-pregnancy care was linked to better glycemic control. They theorised that the decrease in SGA newborns was related to a reduction in congenital abnormalities and the promotion of healthy lifestyles, such as quitting smoking, losing weight, and avoiding teratogenic medicines [208].

4.1.13. Polycythemia

Polycythemia and a rise in nucleated red cells in the cord blood are more common in PGDM than GDM. In type 1 diabetes pregnancies, foetal erythropoietin levels are commonly raised to adjust to prolonged hypoxia by boosting the blood's oxygen-carrying capacity. Low umbilical artery pH (<7.21; $p < 0.0001$), neonatal hypoglycemia ($p = 0.002$), umbilical artery pO2 (< 15.0 mm Hg) ($p < 0.0001$), and foetal macrosomia and growth restriction ($p = 0.004$) were all independently related to amniotic fluid erythropoietin concentration in 156 type 1 diabetic singleton pregnancies at a median time of 1 day [214].

5. Development of Children Born to Mothers with Diabetes

Increased embryonic and foetal oxidative stress is a significant cause of diabetes-induced embryotoxicity and teratogenicity, according to several experimental in vivo and in vitro investigations [29,32,215]. Many researchers have shown that increased oxidative stress in the brain is prevalent in a variety of neurobehavioral and psychiatric illnesses. As a result, it's no surprise that PGDM is linked to a number of neurodevelopmental issues in children. Furthermore, because the cerebral cortex's key developmental processes occur in utero during the third trimester of pregnancy, which is marked by extensive synaptogenesis, dendritic arborization, and neuronal determination [33,216,217], gestational diabetes is likely to have comparable effects. Infants of mothers with PGDM as well as moms with GDM have been documented to have many neurodevelopmental abnormalities connected to maternal diabetes. Furthermore, numerous researchers looked at the postnatal development of infants born to both types of diabetes moms at the same time [8].

5.1. Development of Children Born to Mothers with GDM

Persson and Gentz [218] and Rizzo et al. [159] were among the first researchers to look at the probable neurodevelopmental outcomes of children born to moms with diabetes during pregnancy. They observed no differences in cognitive assessments in children born to mothers with PGDM or GDM.

Later, Ornoy et al. compared the gross and fine motor skills of 32 children aged 6–12 years old who attended normal schools and were born to mothers with GDM, 57 children born to mothers with PGDM, and 57 children born to mothers without GDM to 57 control children [163,164]. When compared to controls, children born to diabetes mothers had substantially poorer Bruininks–Oseretsky fine and gross motor scores. The % of HbA1c, maternal acetonuria, and total motor scores all had a negative link, and the sensory-motor function of infants born to diabetes mothers was worse with greater glycosylated haemoglobin levels. In addition, there was a slightly lower verbal intelligence quotient (IQ) and a greater risk of inattention and attention deficit hyperactivity disorder (ADHD) [8,164].

Torres-Espinola compared the neurodevelopmental outcomes of 79 infants born to women with GDM to 132 control children at the age of six and eighteen months [217]. While the differences between the groups were minor at 6 months—a tiny tendency toward slightly higher language scores—by 18 months, there was a definite trend toward lower motor development scores.

The possibility of minor brain injury in children delivered to mothers with GDM has serious therapeutic implications, as GDM is relatively prevalent, and poorly managed GDM can cause severe metabolic dysfunction, potentially increasing the likelihood of minor developmental problems in offspring.

Ornoy et al. discovered that serum from women with GDM is just as teratogenic as serum from women with PGDM in 10.5-day old rat embryos in culture, generating over 40% of developmental abnormalities [219]. This suggests that the fact that GDM occurs after major organogenesis is the explanation for the lack of a significant rise in the risk of congenital abnormalities. Early GDM start has been linked to an increased risk of congenital abnormalities [27,28]. Furthermore, because the brain grows rapidly throughout pregnancy, GDM-induced metabolic abnormalities may disrupt cerebral hemisphere functioning even in the second half of pregnancy [30].

5.2. Development of Children Born to Mothers with PGDM

IQ test results of children born to mothers with PGDM are often connected to the degree of diabetes

control, and poor glycemic control may be associated with a minor drop in the offspring's intellect. This might explain why some studies have reported normal cognitive performance in offspring of moms with PGDM while others have indicated impaired cognitive function.

5.2.1. Studies Describing Decreased Cognitive Function in Children of Mothers with PGDM

Churchill et al. were among the first to note that infants born to moms with PGDM and acetonuria had worse IQ scores than children born to diabetic mothers who did not have acetonuria and functioned normally [220]. There was no link between IQ and the length of maternal diabetes. Children born to diabetes mothers and who were tiny for gestational age had poorer cognitive scores than controls, according to Stehbens et al. [221]. Similarly, Petersen et al. discovered that SGA children of diabetes moms performed worse verbally at the age of five [222]. Bloch-Petersen also discovered that infants born to diabetes women with low birth weight and preterm had a higher chance of impaired language, speech, and motor development at 4–5 years of age, as measured by the Denver Developmental Screening exam [223]. Kimmerle et al. investigated the development of 36 infants born to women with PGDM and nephropathy (White's class F), ten of whom had renal failure [224]. Seven children (19%) exhibited moderate to severe developmental delays, and one kid (3%) had significant motor impairment [224]. Hod et al. compared the development of 31 one-year-old infants born to moms with type 1 or type 2 PGDM to 41 infants born to non-diabetic mothers and observed lower psychomotor skills [225]. Nelson et al. [226] discovered impaired hippocampal-based recognition memory in diabetic neonates. Their neurodevelopmental scores on the Bayley measures, however, were identical to those of control newborns. The SGA might be a significant confounder, since babies with SGA who do not have maternal diabetes have a range of neurodevelopmental issues [227].

Camprubi Robles et al. included the data from children born to moms with PGDM and those born to mothers with GDM in a meta-analysis of 12–15 studies that documented the neurodevelopment of newborns and children from 1–14 years of age [228]. There were 6140 children in all, ranging in age from one year to fourteen years.

At 1–2 years of age, they discovered a substantial drop in mental scores among infants born to diabetes moms. They also discovered a decrease in IQ in school-aged children born to diabetes mothers, although the data was inconclusive due to substantial variability [228].

5.2.2. Studies That Did Not Find Decreased Cognitive Function in Children of Mothers with PGDM

Many neurodevelopmental investigations on infants born to moms with PGDM who were well-treated found no evidence of cognitive damage. At preschool and early school age, Cummins and Norrish [229], as well as Persson and Gentz [218], found no abnormalities in cognitive scores of children born to diabetes mothers. Rizzo et al. found no developmental delay in children born to mothers with PGDM or GDM, but did find a significant negative correlation between maternal second and third-trimester hydroxybutyrate blood levels and motor development in children aged 6 to 9 years old, with children of mothers with high hydroxybutyrate blood levels having lower scores on the Bruininks-Oseretzky test, which measures fine and gross motor abilities [159]. Sells et al. discovered normal development in 70 babies aged 6–36 months who were born to women with type 1 PGDM who began therapy early [230]. On language tests, however, 39 children born to PGDM moms who began treatment late in pregnancy, had poor diabetes control, and high glycosylated haemoglobin levels performed worse than controls. Compared to 57 age-matched children born to non-diabetic mothers, Ornoy et al. reported normal cognitive performance on the WISC—R in a sample of 57 early school-age children of well-controlled mothers with PGDM [8,163].

Fraser et al. used the huge Swedish national birth registry from 1988–1998 and 1998–2009 to investigate the cognitive capacities of male children born to mothers with PGDM or GDM at the age of 18 [238]. They discovered that maternal PGDM and GDM lowered the intelligence quotient by 1.36 points in non-siblings, but no significant difference was seen among sibling discordant for maternal diabetes. Because no such difference was identified among siblings, the authors concluded that the modest IQ drop observed in non-sibling children born to diabetic mothers is not due to maternal diabetes. The authors further speculate that the negative relationship between siblings might be due to undiagnosed mother diabetes among the "unexposed siblings," and that if these people were included to the exposed group, the difference would be considerable [238].

Boghossian et al. compared the neurodevelopmental outcomes of 536 extremely premature infants (weeks 22–28 of gestation) born to mothers with insulin-dependent diabetes mellitus at 18–22 months corrected age to extremely premature infants born to non-insulin diabetic mothers and found no difference in their neurodevelopmental outcomes [158].

It may be inferred that maternal GDM and PGDM have no effect on the offspring's cognitive performance unless there are diabetes problems that cause considerable foetal development restriction.

6. Diabetes in Pregnancy and ADHD

Nomura et al. examined the development of 21 children born to mothers with GDM to 191 children born to non-diabetic mothers and discovered that children born to moms with GDM had a two-fold incidence of ADHD [231]. Low socioeconomic level (SES) elevated that risk even more, and children with GDM and low SES had worse IQ and linguistic

abilities, as well as a higher likelihood of ADHD [231].

Ornoy et al. discovered a significant prevalence of ADHD in 57 children born to PGDM moms and 32 children born to GDM mothers [8,163,164]. In comparison to controls, children born to diabetic moms had a larger number of failure sores on the Pollack Taper exam, which evaluates attention span and learning capacity, as well as on the Conner's shortened Parent Questionnaire. The prevalence of ADHD was linked to maternal HbA1c levels.

Xiang et al. [232] looked at the risk of ADHD in both PGDM and GDM patients. They looked at the prevalence of ADHD in a large population of children (8344 kids of PGDM moms and 29,534 offspring of GDM mothers) and found no significant increase. When they looked at the rate of ADHD among children born to moms who were treated during pregnancy because they seemed to have more severe PGDM or GDM, they discovered a substantial rise. The Hazard Ratio (HR) for type 1 PGDM was 1.57, for type 2 PGDM was 1.43, and for offspring of women with GDM was 1.26. Children of women with GDM who did not require treatment had an HR of 0.93 [232]. These results are similar to ours [8,163,164] in that they reveal a link between the severity of PGDM and GDM.

Kong et al. investigated the risk of ADHD and ASD (as well as other mental disorders) among the offspring of a large number of mothers with PGDM (4000) and GDM (101,696) with and without obesity using the live birth registry in Finland [233]. The risk of ADHD in kids was very modestly enhanced by maternal PGDM and GDM without obesity (PGDM—HR 1.45; 95 percent CI 0/98–2.19; GDM; HR 1.15, (95 percent CI 1.01–1.30) [238]. Obesity and PGDM in the mother, on the other hand, increased the likelihood of ADHD and conduct disorder (HR = 6.03). ADHD is more common in the kids of women with PGDM and GDM, and the rise is more pronounced in diabetes with complications.

7. Diabetes in Pregnancy and ASD

A considerable number of research on the neurodevelopmental outcome of children born to moms with PGDM or GDM looked at diverse neuropsychiatric issues, such as Autism Spectrum Disorder (ASD). In fact, most studies have found a link between GDM, PGDM, and an elevated risk of ASD in children [239].

Lyall et al. looked examined the probable link between maternal GDM and ASD in 793 ASD children from a cohort of 66,445 pregnancies and reported an OR of 1.76 [236]. Gardener et al. discovered that maternal diabetes was one of the top variables related with ASD, with an odds ratio of 2.07 (95 percent CI 1.24–3.47) [237], when investigating probable correlations of a number of prenatal maternal factors with ASD. A similar link has been discovered in a number of other investigations. In a study comparing the children of 12,642 women with gestational diabetes to 218,629 non-diabetic mothers, Nahum Sacks et al. discovered an adjusted odds ratio of 4.4 (95 percent confidence interval: 1.55–12.69) for ASD [240]. Using the Boston Birth Cohort, Li et al. discovered that both maternal PGDM and obesity were strongly linked to ASD in the kids. The hazard ratio (HR) for ASD was 3.91 (95 percent confidence interval: 1.76–8.68), whereas the HR for obesity and GDM was 3.04 (95 percent confidence interval: 1.21–7.63) [234]. Kong et al. identified an HR of 3.64 for maternal PGDM and obesity and an HR of 1.56 for maternal GDM and obesity in their analysis utilising the Finnish birth registry [233].

Several studies have also revealed no link between diabetes during pregnancy and ASD. Hultman et al., for example, observed a connection between ASD and a range of pregnancy-related variables but not maternal diabetes in their case–control analysis of 408 Swedish infants with ASD compared to 2040 matched controls [241]. In a study of pregnant women with type 2 diabetes, Xiang et al. discovered an insignificant connection between PGDM and ASD, with an OR of 1.21 [242]. The HR was significant—1.42 (95 percent CI 1.15–1.74) in the children of mothers with GDM diagnosed before the 26th week of pregnancy and typically more severe. Kong et al. discovered no link between non-obese mothers' PGDM or GDM and ASD in their children.

Guinchat et al. found no evidence of a robust link between maternal hyperglycemia and ASD in their assessment of 85 studies [243]. Xu and colleagues, in contrast to their evaluation, removed twelve studies [235]. The pooled risk of maternal diabetes (GDM and PGDM) was 1.48 (1.25–1.75, $p < 0.001$) in the three cohort studies, and 1.72 (1.24–2.41, $p = 0.001$) in the nine case-control studies. Although significant, the OR for children of mothers with GDM was often smaller than that of mothers with PGDM [235]. The mechanism behind the link between diabetes and autism spectrum disorder is mainly unclear. It's important to recall that the higher risk identified might be linked to a range of pregnancy issues that are frequent in diabetic women, and there's a link between pregnancy difficulties and ASD in the children [9,239]. According to the proposed mechanisms of maternal diabetes's effects on the embryo and foetus, the increased rate of ASD in diabetic pregnancies could be due to increased foetal oxidative stress, epigenetic changes in the expression of several genes, or other neuro-developmental changes induced by maternal diabetes [9]. The best method to minimise diabetic-related ASD is probably to maintain optimal glycemic control [239,242].

8. Conclusions

Diabetes, like numerous other maternal chronic disorders in pregnancy, has the potential to have a major unfavourable influence on the developing embryo and baby, as well as on the course of the pregnancy. PGDM is thought to be more harmful to the developing embryo and foetus than GDM, but poorly controlled GDM, especially if other risk factors such as obesity are present, may also harm

the foetus, causing similar perinatal complications such as changes in growth pattern, neurodevelopmental deviations, and, apparently, an increased rate of congenital malformations as a result of early glucose intolerance. The major etiologic cause underlying all of these issues appears to be hyperglycemia, as strict glycemic management alleviates many of these symptoms. Even the best diabetes control, however, does not guarantee that all problems will be avoided. The best treatment for diabetes appears to be prevention. Unfortunately, as a result of poor lifestyle choices, we have seen a steady increase in the rate of diabetes over the previous two decades, with a corresponding decrease in the age of start. We appear to have a good understanding of how to put out a fire, but it appears that preventing one is far more difficult.

Abbreviations

T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
GDM	gestational diabetes mellitus
PGDM	pre-gestational diabetes mellitus
HbA1c	glycosylated hemoglobin
AVS	atrioventricular septal
aOR	adjusted odds ratio
CI	confidence interval
RR	relative risk
HR	hazard ratio
PI	ponderal index
hCG	human chorionic gonadotropin
hPL	human placental lactogen
hPGH	human placental growth hormone
PGH	Placental growth hormone
IGF-I	insulin-like growth factor I
IGFBPs	IGF binding proteins
IGFBP1	IGF binding protein 1
apo-M	apolipoprotein M
TNF-α	tumor necrosis factor-α
GC/MS	gas chromatography/mass spectrometry
LC/MS	liquid chromatography/mass spectrometry
IUGR	intrauterine growth retardation
Glut	glucose transporter proteins
GWG	gestational weight gain
LGA	large for gestational age
SGA	small for gestational age
AGA	Appropriate for Gestational Age
VLBW	very low birth weight
FGR	fetal growth restriction
GHBP	growth hormone-binding protein
BMI	body mass index
IQ	intelligence quotient
ACOG	the American College of Obstetricians and Gynecologists
EFW	estimated fetal weight
US	ultrasound
NICU	neonatal intensive care unit
ROP	retinopathy of prematurity
RDS	respiratory distress syndrome
PDA	patent ductus arteriosus
EOS	early-onset sepsis
IVH	intraventricular hemorrhage

PVL	periventricular leukomalacia
BPD	bronchopulmonary dysplasia
UA	umbilical artery
IADPSG	Diabetes and Pregnancy Study Group
NICE	National Institute for Health and Care Excellence
SES	socio-economic status
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder

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