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THE RISK OF GESTATIONAL DIABETES IN PREGNANCY.

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Abstract

Diabetes can be characterized as heterogeneous group of metabolic disorders which are characterized by defects in insulin resistance and insulin secretion or both. Gestational diabetes is one of the metabolic disorders which is classified under this heading and specifically occurs during pregnancy. According to data found in 2017 almost 7% of pregnant women develop gestational diabetes and 1 in 6 births are affected due to complications of gestational diabetes. About 343 million women are estimated to suffer from GSD till 2045 and GSD affects nearly 14% of pregnancies worldwide which represents approximate 18 million births over the year.

The complications associated with GSD can be severe and affect the mother as well as the baby resulting in life long disorders, malformations and risk to mother's life. In this review we are going to see all those complications that occur due to the conditions caused by GSD and also how they can be prevented.

Introduction

For understanding what is gestational diabetes one has to understand the category under which it is classified as a whole, that is diabetes mellitus. Diabetes mellitus is categorized as heterogeneous group of metabolic disorders which result in hyperglycemia and defects in insulin functioning and sensitivity.

Understanding Diabetes mellitus

Diabetes mellitus can be categorized as heterogeneous group of metabolic disorders resulting in hyperglycemia and defects in insulin function it can be either secretion or generated resistance to identify insulin [1]

When insulin arrives to transporter it attaches itself to specific receptors and the channel opens for glucose metabolism which on later stage provides energy to the cell, in humans glucose tolerance is maintained because of the balance between both the functions that is insulin secretion and insulin sensitivity[2] In individuals with the equal degree of glucose tolerance, the product of insulin sensitivity and insulin secretion remains constant [4] that is the secretory response of pancreatic β cells to glucose and the sensitivity of the glucose utilizing tissues to insulin remains constant[3]

During pregnancy a female goes through a lot of variations because of number of hormones that are secreted in the body for maintaining healthy pregnancy. The hormones so secreted lead to insulin resistance which indeed increases insulin resistance.

What is Gestational Diabetes?

Gestational diabetes mellitus (GDM) is a form of diabetes that is first recognized during pregnancy, with no evidence of pre-existing type 1 or type 2 diabetes.

There are two classes of gestational diabetes.

i)Women with class A1 can manage it through diet and exercise.

ii) Women with class A2 need to take insulin or other medications.

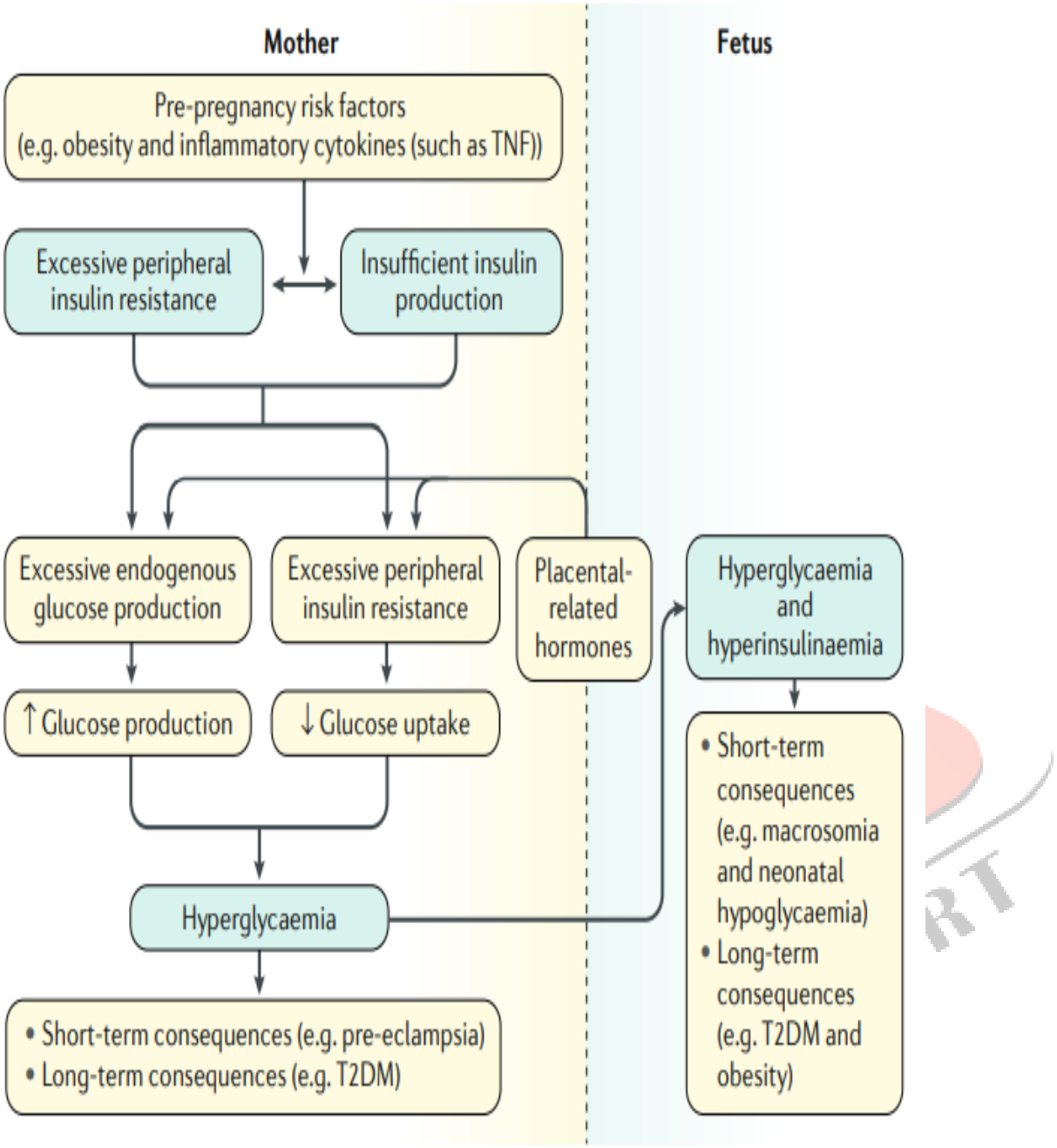
Pathophysiology

- Pancreatic β-cell defects and increased insulin resistance.
- With the onset of pregnancy and associated metabolic changes (increased insulin resistance and demand for increased β-cell response because of placental factors), insulin is less effective in suppressing endogenous (primarily hepatic) glucose production and glucose uptake by peripheral skeletal muscle and adipose tissue, which results in clinical hyperglycaemia.

- **Pathogenesis of gestational diabetes**

  The pathogenesis of GDM has been extensively studied by Catalano et al. using euglycaemic hyperinsulinemic clamp techniques and glucose infusion. The conclusion he reported is that women who develop GDM are before pregnancy insulin resistant 1compared to women who did not develop diabetes during pregnancy (1). The significant decrease in insulin sensitivity in late gestation reflects the decreased insulin sensitivity that exists prior to pregnancy (2). In addition, defects in insulin secretion have been reported during pregnancy and related to the degree of glucose intolerance (3). After, delivery b-cell dysfunction persists and is also correlated with the severity of glucose intolerance during pregnancy (4,5).

- In GDM, circulating TNFa and interleukin 6 (IL6) has been inversely correlated with insulin sensitivity suggesting a role of inflammatory factors in the pathogenesis (6, 7). Other cytokines such as leptin have been found elevated in GDM (8). However, the main determinant of leptin during pregnancy is the pre-gravid maternal weight (9). After pregnancy, insulin sensitivity returns to pre-gravid values (10). Like all forms of hyperglycaemia, GDM is characterized by insulin secretion that is insufficient to meet insulin demands. Thus, pregnancy represents a situation in which undiagnosed diabetes, or rather unknown b-cell failure, is revealed by the physiological occurrence of insulin resistance.



Aetiologies of GSD

Type 2 Diabetes

GDM is most commonly a forerunner of T2D (11). In a meta-analysis from Bellamy et al. (11), women with GDM have a sevenfold risk of T2D for several years compared to women with normal glucose tolerance (NGT) during pregnancy. Longitudinal studies longer than 10 years indicate that more than 25% of GDM will develop T2D (12, 13). Women with GDM display insulin resistance before and after pregnancy as in predisposed T2D subjects (14). GDM is found to carry more T2D risk alleles. Lauenborg et al. have shown a strong association between ten of 11 studied T2D risk alleles and a history of GDM (15). A genome-wide association study performed from the HAPO study shows that among the susceptibility genes, variants of

glucokinase (GCK) and TCF7L2 loci are associated with higher glucose levels during oral glucose tolerance tests in pregnant women (16)

Monogenic diabetes

Monogenic form of diabetes may also be revealed during pregnancy. It has also been shown that common variants in maturity onset diabetes of the young (MODY) genes contribute to GDM, like polymorphism of the promoter of GCK and polymorphism of Hepatocyte nuclear factor 1a (HNF1a) (17). MODY refers to any of the several forms of hereditary diabetes caused by mutations in an autosomal dominant gene influencing insulin production. One of these forms is MODY 2, which seems to be the most frequently associated with GDM, with a prevalence of around 10% of GDM (18). It is due to mutations of the GCK gene (19). Ellard et al. (20), from the UK, reported 12 out of 15 GDM having MODY 2. In this study, the extremely high prevalence of MODY 2 was due to the fact that genotyping was performed in phenotypically preselected women. They all had an abnormal fasting glucose outside pregnancy with a low increment between the fasting and 2-h plasma glucose concentrations on 75 g OGTT. Additionally, included women were insulin treated during at least one pregnancy and they had a history of T2D, GDM or fasting hyperglycaemia in a first-degree relative. Few MODY 3 and MODY 4 have also been reported in GDM women (21,22).

Type 1 diabetes

Auto-immune diabetes may also be considered as aetiology of GDM. The prevalence of auto-immune markers of type 1 diabetes (T1D) is between 0.98 and 14.7% in women with GDM. It predicts later development of T1D in these women but not necessarily (47). In some studies (48, 49), positive islet cell autoantibodies were not predictive of future diabetes development. Thus GDM may reveal T1D but whether or not antibodies need to be tested in GDM deserves further studies. Autoimmunity was associated with poor pregnancy outcomes (fetal death, preterm delivery and macrosomia) (50)

Insulin resistance, β cell dysfunction, and GDM

The majority of women with GDM appear to have β cell dysfunction that occurs on a background of chronic insulin resistance. As noted above, pregnancy normally induces quite marked insulin resistance. This physiological insulin resistance also occurs in women with GDM. However, it occurs on a background of chronic insulin resistance to which the insulin resistance of pregnancy is partially additive. As a result, pregnant women with GDM tend to have even greater insulin resistance than normal pregnant women. Differences in whole-body insulin sensitivity tend to be small in the third trimester, owing to the marked effects of pregnancy itself on insulin resistance. Nonetheless, precise and direct measures of insulin sensitivity applied during the third trimester have identified, in women with GDM, exaggerated resistance to insulin's ability to stimulate glucose utilization (17, 18) and to suppress both glucose production (17, 18) and fatty acid levels (17). After delivery, when the acquired insulin resistance of pregnancy abates, women who had GDM end up, on average, with considerably greater insulin resistance than normal women. This finding, which has been consistent across studies in which whole-body insulin sensitivity has been measured directly (22, 23, 25, 26, 37–40), indicates that most women who

develop GDM have chronic insulin resistance. Sequential measurements of insulin sensitivity performed in the same women before pregnancy, early in the second trimester, and in the third trimester have documented insulin resistance in both lean and obese women who go on to develop GDM (18, 24). Only a small number of potential biochemical mediators of the chronic insulin resistance that frequently accompanies GDM and that likely contributes to the high risk of type 2 diabetes have been examined. It is likely that there is not a single underlying biochemical etiology. Women with GDM tend to be obese, so mechanisms promoting obesity and/or linking obesity to insulin resistance are likely to play a role. Small studies have revealed increased circulating levels of leptin (41) and the inflammatory markers TNF-α (42) and C-reactive protein (43) and decreased levels of adiponectin (44, 45) in women with GDM. Increased content of fat in liver (46) and muscle (47) has also been reported in women with previous gestational diabetes. All of these findings are consistent with the current understanding of some potential causes of obesity-related insulin resistance. Defects in the binding of insulin to its receptor in skeletal muscle do not appear to be involved in the exaggerated insulin resistance of GDM (48). Alterations in the insulin signaling pathway (49–52), abnormal subcellular localization of GLUT4 transporters (53), reduced expression of PPARγ (49), increased expression of the membrane glycoprotein PC-1 (51), and reduced insulin-mediated glucose transport (52, 53) have been found in skeletal muscle or fat cells of women with GDM or a history thereof compared with normal women. Whether any of these defects is primary or the result of more fundamental defects in insulin action is currently unknown.

Given that GDM represents a cross-section of young women with glucose intolerance, mechanisms that lead to chronic insulin resistance in GDM are likely to be as varied as they are in the general population. It has long been thought (and taught) that GDM develops in women who cannot increase their insulin secretion when faced with the increased insulin needs imposed by late pregnancy. Serial studies of women who develop GDM do not support that concept. As illustrated in Figure 1, insulin secretion in obese women who develop GDM can increase considerably over weeks or months in association with the acquired insulin resistance of pregnancy. However, the increase occurs along an insulin sensitivity-secretion curve that is approximately 50% lower (i.e., 50% less insulin for any degree of insulin resistance) than that of normal women.

These short-term responses appear to occur on a background of long-term deterioration of β cell function that, over years, leads to progressive hyperglycaemia and diabetes . Longitudinal studies of lean and obese women before pregnancy, at the beginning of the second trimester, and in the third trimester also reveal an increase in insulin secretion in association with the acquired insulin resistance of pregnancy (18, 24). However, the increase is less than that which occurs in normal pregnant women despite somewhat greater insulin resistance in individuals with GDM. These small but elegant physiological studies reveal that the limitation in insulin secretion in women with GDM is not necessarily fixed. Rather, in at least some of them, insulin secretion is low relative to their insulin sensitivity but responsive to changing sensitivity. One approach to the prevention of diabetes after GDM has taken advantage of this responsiveness (discussed below in “Link to diabetes after pregnancy”). Very little is known about the genetics of GDM in women

with chronic insulin resistance. The few studies that have been done have compared allele frequencies of candidate genes in women with and without GDM, with no selection for specific phenotypic subtypes of GDM. Variants that differed in frequency between control and GDM subjects were found in genes coding for: (a) the islet-specific promoter of glucokinase (54), known to be important for glucose sensing by β cells; (b) calpain-10 (55), a gene associated with type 2 diabetes in Hispanic Americans and some other ethnic groups; (c) the sulfonylurea receptor 1 (56), which is involved in glucose-stimulated insulin secretion; and (d) the β3 adrenoreceptor, which may regulate body composition. Whether these findings will be confirmed in larger studies with broader representation among women with GDM remains to be determined.

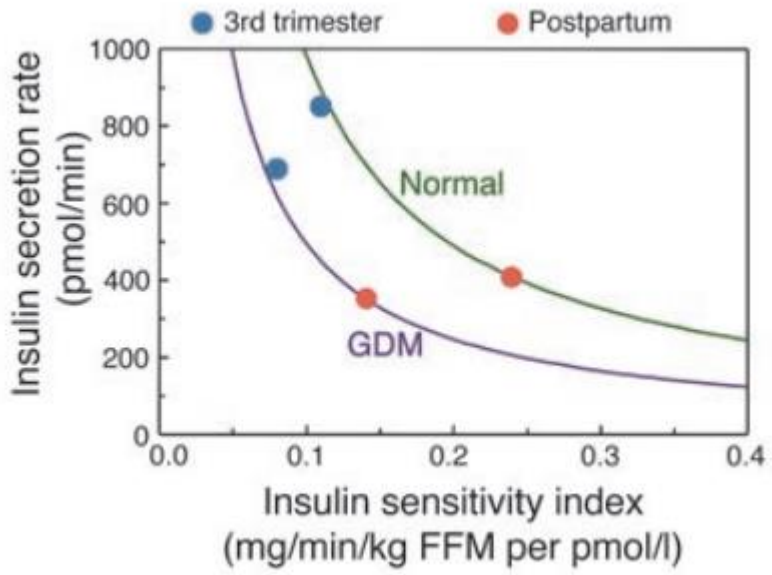


Figure : Insulin sensitivity-secretion relationships in women with GDM and normal women during the third trimester and remote from pregnancy. Values were measured at the end of 3-hour hyperglycemic clamps (plasma glucose, about 180 mg/dl) (22). Prehepatic insulin secretion rates were calculated from steady-state plasma insulin and C-peptide levels. Insulin sensitivity index was calculated as steady-state glucose infusion rate divided by steady-state plasma insulin concentration. FFM, fat-free mass.

Link to diabetes after pregnancy

The hyperglycaemia of GDM is detected at one point in a women's life. If glucose levels are not already in the diabetic range, GDM could represent glucose intolerance that is limited to pregnancy, is chronic but stable, or is at a stage in the progression to diabetes. Long-term follow-up studies, recently reviewed by Kim et al. (57), reveal that most, but not all, women with GDM do progress to diabetes after pregnancy. Only approximately 10% of patients have diabetes soon after delivery (58). Incident cases appear to occur at a relatively constant rate during the first 10 years thereafter (57), and the few studies that have been conducted over a period of more than 10 years reveal a stable long-term risk of approximately 70% (57). Most studies of risk factors for the development of diabetes after GDM fail to distinguish among the possible subtypes of

GDM and diabetes discussed above. They generally reveal risk factors, such as obesity, weight gain, and increased age, that are known to be associated with type 2 diabetes. Relatively high glucose levels during and soon after pregnancy also correlate with increased risk of diabetes, perhaps because they identify women who are relatively close to developing diabetes when the diagnosis of GDM is made

Those studies have revealed much about the β cell defect that leads to type 2 diabetes after GDM in 1 ethnic group. First, weight gain and additional pregnancies, factors associated with chronic and acute insulin resistance, respectively, independently increase the risk of developing diabetes (59). Second, decreasing β cell function is associated with increasing hyperglycemia (Figure 2) (60). The impact of reduced β cell function on glucose levels is relatively small until the disposition index, which reflects acute insulin responses to glucose in relation to insulin resistance, is very low (approximately 10–15% of normal). Thereafter, relatively small differences in β cell function are associated with relatively large increases in glucose levels (60). Third, treatment of insulin resistance at the stage of impaired glucose tolerance results in a reciprocal downregulation of insulin secretion (61), which in turn is associated with a reduction in the risk of diabetes and with preservation of β cell function (62). Taken together, these 3 findings reveal a progressive loss of insulin secretion that appears to be caused by high insulin secretory demands imposed by chronic insulin resistance

Causes

The two major causes of Gestational Diabetes are

1) **Hormones**

During pregnancy, placenta makes hormones that cause glucose to build up in your blood for nourishment of baby

Pregnancy hormones like placental lactogen can interfere with susceptible insulin receptors, which further increases blood glucose levels.

Usually, your pancreas can send out enough insulin to handle it. But if your body can't make enough insulin or stops using insulin as it should, your blood sugar levels rise, and you get gestational diabetes.

When the amount of insulin produced is less than the amount needed to handle blood glucose levels, gestational diabetes can arise

Human Placental Lactogen:

2) **Placental Lactogen**

Placental Lactogen also known as chorionic somatotropin, is a peptide hormone produced during pregnancy, in humans and other animals, by specialized endocrine cells.

It plays an important role in the regulation of insulin secretion in pancreatic β-cells, stimulating their proliferation and promoting the expression of anti-apoptotic proteins.

It is secreted throughout pregnancy by both animal and human specialized endocrine cells. PL plays an important role in the regulation of insulin secretion in pancreatic β-cells, stimulating their proliferation and promoting the expression of anti-apoptotic proteins.

Cases of pregnancy affected by metabolic conditions, including obesity and diabetes, are related to alterations in the PL secretion pattern. Whereas obesity is most often associated with lower PL serum concentrations, diabetes results in increased PL blood levels. Disruptions in PL secretion are thought to be associated with an increased prevalence of gestational complications, such as placental dysfunction, diabetic retinopathy, and abnormalities in fetal growth.

PL is believed to be positively correlated with birth weight. The impaired regulation of PL secretion could contribute to an increased incidence of both growth retardation and fetal macrosomia. Moreover, the dysregulation of PL production during the intrauterine period could affect the metabolic status in adulthood. PL concentration measurement could be useful in the prediction of fetal macrosomia in women with normal oral glucose tolerance test (OGTT) results or in evaluating the risk of fetal growth restriction, but its application in standard clinical practice seems to be limited in the era of ultrasonography.

Role in Pancreatic Beta Cells

Members of the PL family hormones, such as prolactin and PL, are regarded as stimulators of the intensive proliferation of pancreatic β-cells in pregnant rodents. However, the proliferative effect of prolactin on human β-cells in vitro was not as spectacular as that observed in rodents [40]. The possible mechanism of the proliferative effect of endogenic PL on pancreatic islets is closely associated with the stimulation of prolactin receptors in rodent β-cells. Transgenic mice with a specific deletion of PRLR from β-cells exhibit reduced β-cell expansion during pregnancy, leading to the development of gestational diabetes [41]. Human studies suggest that lactogens are less effective in the regulation of beta cell adaptations to pregnancy. For example, Nalla et al. collected serum samples from pregnant (early and late pregnancy) and non-pregnant women [42]. Subsequently, the effect of the sample administration was examined on rat neonatal β-cells and the rat insulinoma cell line. The most potent mitogenic effect was observed in samples exposed to late pregnancy sera. Isolated proliferative fractions contained PL, kininogen-1, fibrinogen-α-chain, α1-antitrypsin, apolipoprotein-A1, angiotensinogen, and serum albumin. Furthermore, the authors also discovered that the fractions had an inhibiting effect on insulinoma cell proliferation, suggesting that the activity of those factors could significantly contribute to the regulation of metabolic adaptations throughout pregnancy [42]. PL not only promotes β-cell proliferation but can also effectively inhibit apoptotic activity in murine and rat insulinoma cell lines through the phosphorylation of protein kinase B (AKT), as shown in Figure 1. The anti-apoptotic effect of PL was also observed in human pancreatic islet cells in vitro [43]. Cultured islets, treated with PL solution, secreted increased amounts of pancreatic and duodenal homeobox 1 (PDX1), which is an essential factor in pancreatic development [44]. The treatment resulted in improved glucose-induced insulin secretion compared with unstimulated control cells [43].

Furthermore, it has been reported that lactogens could protect pancreatic cells against glucolipotoxicity, which normally leads to beta cell death [45]. The next protective mechanism of lactogens was demonstrated in vitro in rat insulinoma cells and primary mouse beta cells exposed to prolactin treatment with the presence of dexamethasone, which is recognized as a beta cell apoptotic inducer. Beta cell death, mediated by exposure to dexamethasone, was significantly reduced in cell cultures treated with PRL. The reduction in beta cell deaths is believed to be related to the activity of the Janus-activated-kinase-2/signal transducer and activator of transcription-5 (JAK2/STAT5) pathway. Furthermore, lactogens participate in the expression of the Bcl-XL anti-apoptotic protein, the presence of which is required, independently of the JAK2/STAT5 pathway, to enhance their protective activity in rodent cells [46].

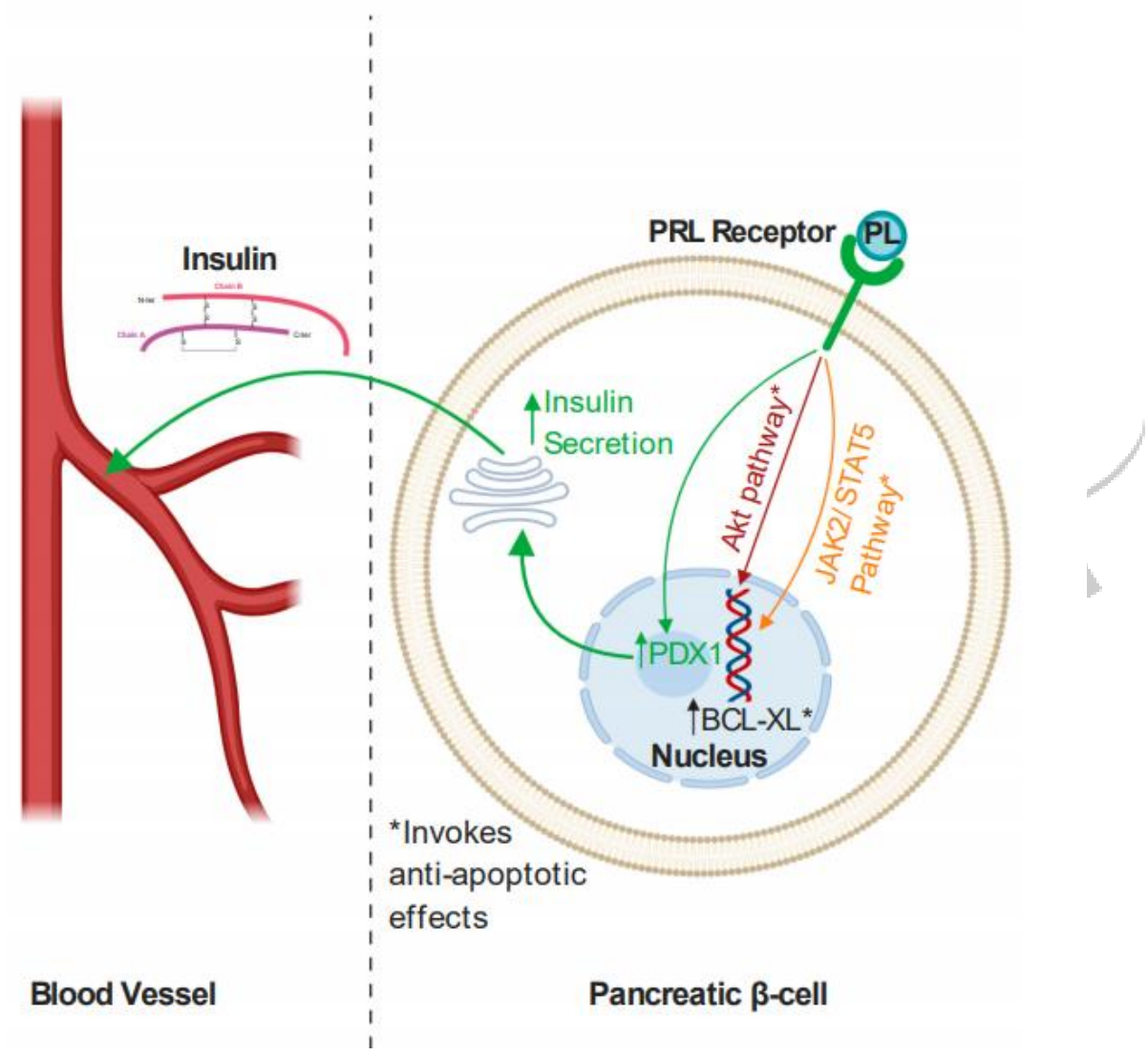


Figure 2 The mechanisms of the biological activity of placental lactogen (PL) in pancreatic β-cells. PL binds to the prolactin receptor (PRL Receptor) to promote increased insulin secretion through the stimulation of pancreatic and duodenal homeobox 1 (PDX1) expression. PL also activates a range of intracellular pathways (the Janus-activated-kinase-2/signal transducer and activator of transcription-5 (JAK2/STAT5) pathway and the phosphorylation of protein kinase B (AKT)) to protect β-cells from apoptotic death. Independently from the mechanisms

mentioned above, PL contributes to increased expression of the BCL-XL anti-apoptotic protein [43–46]. Created with BioRender.

Finally, PL is responsible for the regulation of gestational adaptations of maternal pancreatic beta cells, which can prevent the development of glucose intolerance during pregnancy [40,41]. Moreover, it simultaneously acts as a stimulator of beta cell proliferation and has an anti-apoptotic effect on islet beta cells. However, it is important to mention that its proliferative effect on the population of human beta cells is less pronounced [40–43,45,46].

Other risk factors

Maternal factors

- Older age
- High parity Pre-pregnancy weight
- Pregnancy weight gain
- BMI = 27
- Short stature
- Low birth weight
- α-Thalassaemia trait
- Polycystic ovary syndrome
- High intake of saturated fat

Family history

- Family history of diabetes
- GDM in woman's mother
- Previous obstetric outcome
- Congenital malformation
- Stillbirth Macrosomia
- Caesarean section
- Previous GDM

Pregnancy factors

- High blood pressure in pregnancy
- Multiple pregnancy
- Increased iron stores

Protective factors

- Young age
- Alcohol use

Polycystic ovary syndrome

Polycystic ovary syndrome and GDM Polycystic ovary syndrome (PCOS) is a heterogeneous disorder affecting 5–10% of women of reproductive age. It is characterized by chronic anovulation with oligo/amenorrhoea, infertility, typical sonographic appearance of the ovaries, and clinical or biochemical hyperandrogenism; insulin resistance is present in 40–50% of patients, especially in obese women [28]. Holte et al. [29] reported a higher rate of ultrasonographic, clinical and endocrine signs of PCOS in 34 women who had had GDM 3–5 years before, compared with 36 matched controls with uncomplicated pregnancies. They concluded that women with previous GDM and PCOS may form a subgroup distinct from women with normal ovaries and previous GDM characterized by a stronger tendency to develop features of insulin resistance syndrome. Many other researchers reported similar results [30–33]. Some suggested a screening programme for GDM for these patients. PCOS is considered as a prediabetic state, associated with a 31–35% prevalence of IGT and a 7.5–10% prevalence of Type 2 diabetes [34]. The conversion rate from IGT to overt Type 2 diabetes is increased five- to 10-fold in women with PCOS [35].

Multiple pregnancy and GDM

The number of fetuses in multifetal pregnancies may influence the incidence of GDM owing to the increased placental mass and, thereby, the increase in diabetogenic hormones. However, reports are somewhat conflicting, probably because of the heterogeneous populations studied. In an interesting study of the prevalence of GDM in dizygotic (DZ) twin pregnancies with two placentas compared with monozygotic (MZ) twin pregnancies with one placenta, Hoskins et al. [36] found that a higher proportion of different sex rather than same-sex twin pregnancies was complicated by GDM (3.5% vs. 1.6%). The impact of fetal reduction (selective feticide of one or more fetuses in high-order multiple pregnancies) on the incidence of GDM may also support this theory. Sivan et al. [37] found that the rate of GDM was significantly higher in the triplet group than in the reduction group (22.3% vs. 5.8%). Similar results were reported by Schwartz

et al. [38], who showed that GDM was significantly more frequent in twin deliveries (7.7% vs. 4.1%, P < 0.05). However, insulin requirements were not different, suggesting a minor clinical impact. By contrast, using data derived from the Medical Birth Registry of Norway, Egeland and Irgens [39], controlling for other risk factors such as advanced age, parity, maternal history of diabetes, and woman's own birth weight, found no elevated risk of GDM among 9271 multifetal pregnancies. Others havealso failed to demonstrate a higher prevalence of GDM in multiple pregnancies [40,41].

Recurrence of GDM

MacNeill et al. [42] found a 35.6% recurrence rate of GDM. Multivariate regression models showed that infant birth weight in the index pregnancy and maternal weight before the subsequent pregnancy were predictive of recurrent GDM. Higher recurrence rates (69% of 78 patients) were reported by Major et al. [43]. Recurrence was more common when the following variables were present in the index pregnancy: parity ≥ 1 [odds ratio (OR) = 3.0], BMI ≥ 30 kg/m2 (OR = 3.6), GDM diagnosis at ≤ 24 gestational weeks (OR = 20.4), and insulin requirement (OR = 2.3). A weight gain of ≥ 7 kg (OR = 2.9) and an interval between pregnancies of ≤ 24 months (OR = 1.6) were also associated with a recurrence of GDM. Spong et al. [44] found a similarly high recurrence rate of 68% in 164 women with GDM. Risk factors for recurrence in this study were earlier diagnosis of GDM, insulin requirement, and hospital admissions in the index pregnancy.

IGT as a risk factor of adverse outcome The cut-off level of glycaemia beyond which the risk of an adverse outcome of pregnancy is increased is of major clinical importance in the management and initiation of therapy. Nasrat et al. [45] (Saudi Arabia) examined pregnancy outcome in 212 women with IGT and 212 women with normal glucose tolerance, and concluded that IGT does not lead to any adverse outcome. Similar findings were reported by Ramtoola et al. [46] (Mauritius), who failed to find an excess perinatal mortality in 267 pregnant women with IGT compared with a background population. By contrast, Moses and Calvert [47] (Australia) suggested that the clinically optimal level for glycaemia during pregnancy should be as near to normal as possible. They studied the proportion of assisted deliveries and the proportion of infants admitted to special care in relation to the range of glucose tolerance, and found an association between glycaemia and both outcomes. Conflicting results were also reported by others. Al-Shawaf et al. [48] (Saudi Arabia) found that women with gestational IGT were older and more obese, and had higher parity, and heavier babies than pregnant women with normal screening plasma glucose, and Roberts et al. [49] (UK) found no significant difference in the incidence of antenatal complications between mothers with normal and impaired glucose tolerance (n = 135 each). Although the IGT group had a higher rate of induced labour and caesarean section, there was no betweengroup difference in fetal outcome or neonatal morbidity. Tan and Yeo [50] (Singapore), in a retrospective analysis of 944 women with IGT in pregnancy (8.6%) and 10 065 women with normal pregnancy, noted that even when maternal age and obesity were excluded, the IGT group had a significantly higher risk of labour induction, caesarean section, caesarean section for dystocia/no progress, fetal macrosomia, and shoulder dystocia. The risk of hypertensive disease and caesarean section for fetal distress/thick

meconium-stained amniotic fluid were also higher in the IGT group, but the differences were not statistically significant when maternal age and obesity were excluded. There was no significant difference in the rates of low Apgar scores at 1 and 5 min between the two groups. It is possible that some of the adverse outcomes associated with excess maternal weight were in fact related to GDM. It is also possible that some of the complications attributed to GDM, especially the milder form of IGT, were actually related to excess maternal weight. Jacobson and Cousins [51] (USA) reported that good glycaemic control did not normalize birth weight percentiles, and maternal weight at delivery was the only significant predictor of birth weight percentile. Thus, IGT diagnosed for the first time in pregnancy might only be a feature of excess maternal weight and not in itself a pathological condition. The clinical significance of IGT has also been disputed [Nasrat et al. [45] (Saudi Arabia), Li et al. [52] (Hong Kong)]. Lao and Ho [53] (China) also concluded that some of the complications attributed to GDM are probably related to maternal obesity, but IGT could still affect infant birth weight despite dietary treatment that normalizes maternal gestational weight gain. In another recent study [54] (Denmark) of 2904 pregnant women, the following outcomes measures increased significantly with increasing glucose values on the OGTT: shoulder dystocia, macrosomia, emergency caesarean section, assisted delivery, hypertension, and induction of labour. However, when corrections were made for other risk factors, hypertension and induction of labour were only marginally associated with glucose levels. Aberg et al. [55] (Sweden) conducted a population-based study of maternal and neonatal characteristics and delivery complications in relation to findings for the 75-g, 2-h OGTT at 25–30 weeks' gestation. An increased rate of caesarean section and infant macrosomia was observed in the group with a glucose tolerance of 140–162 mg/dl (7.8–9 mmol/l) and in the GDM group. Advanced maternal age and high BMI were found to be risk factors for increased OGTT values.

Abnormal GCT as a risk factor for adverse pregnancy outcome

Is an abnormal GCT alone, without GDM, a risk factor for adverse pregnancy outcome? Using fetal weight and anthropometric characteristics as their parameters, Mello et al. [56] evaluated 1615 white women with singleton pregnancies who underwent universal screening for GDM in two periods of pregnancy. They divided the population into three groups according to the GCT results:

(i) 172 patients with an abnormal GCT in both periods;

(ii) (ii) 391 patients with a normal GCT in the early period and an abnormal GCT in the late period;

(iii) (iii) 1052 patients with a normal GCT in both periods (control group). The incidence of large-for-gestational-age (LGA) infants was significantly higher in group 1 (40.7%) and group 2 (22.0%) than in the control group (8.3%), and significantly higher in group 1 than group 2. The new-borns of group 1 had a higher birth weight than those of group 2 and the control group, and the new-borns of the control group had significantly greater length and mean cranial circumference. Group 1 babies had a significantly lower ponderal index, thoracic circumference, and weight/length ratio than controls, and a significantly larger cranial/thoracic circumference. To determine the predictive value of a negative GCT in

subsequent pregnancies, Nahum [57] studied 62 pregnancies of women who had given birth twice during the past 4 years and for whom third-trimester 1-h 50-g glucose screening test results were available for both pregnancies. He found that the GCT results were significantly correlated between the two pregnancies ($r = 0.49$, $P < 0.001$) and concluded that a negative GCT of < 140 mg/dl (7.8 mmol/l) during pregnancy is strongly predictive of a negative screening result in a succeeding pregnancy within 4 years. Accordingly, it is possible that abnormal GCT alone, even without GDM, is a prediabetic state at the lower spectrum of insulin resistance (Fig. 1), and should be regarded as a risk factor for pregnancy complications, such as fetal macrosomia. However, in clinical practice we do not use this factor for obstetric management.

Early GDM diagnosis as a risk factor for Type 2 diabetes

Early diagnosis of GDM, that is, in the first half of pregnancy, is a high risk factor for future development of Type 2 diabetes. Bartha et al. [58] found that among 3986 pregnant women, those with early-onset GDM (n = 65) were more likely to be hypertensive (18.46% vs. 5.88%; $P = 0.006$) and had higher glycaemic values and greater need for insulin therapy (33.85% vs. 7.06%, $P < 0.001$) than those in whom diabetes developed later (n = 170). All cases of neonatal hypoglycaemia (n = 4) and all perinatal deaths (n = 3) were in this group. The women with early GDM also had an increased risk of postpartum diabetes mellitus, whereas those with late-onset GDM had a minimal risk [59]. The percentages of overt diabetes and abnormal glucose tolerance were significantly higher in the early pregnancy group (n = 30) than in the late-pregnancy group (n = 72) (26.7% vs. 1.4% and 40% vs. 5.56%, respectively).

Congenital malformations

Schaefer-Graf et al. [60], in a review of 4180 pregnancies complicated by GDM (n = 3764) or Type 2 diabetes (n = 416), reported that the congenital anomalies in the offspring affected the same organ systems described in pregnancies complicated by Type 2 diabetes. The risk of anomalies rose with increasing hyperglycaemia at either diagnosis or presentation for care. However, most other reports had conflicting findings. Bartha et al. [58] failed to find an increase in major congenital malformations associated with GDM, as did Kalter [61] in acomprehensive review of the literature. An exception is the recent Swedish Health Registry study covering over 1.2 million births in 1987–1997 [62]. The authors identified 3864 infants born to women with pre-existing diabetes and 8688 infants born to women with GDM. The total malformation rate in the first group was 9.5%, and in the second group, 5.7%— similar to the rate in the general population. However, the GDM group was characterized by an excess of certain malformations, suggesting that a subgroup of GDM patients are at increased risk of diabetic embryopathy, perhaps due to pre-existing but undetected Type 2 diabetes. Martinez-Frias et al. [63] analysed 19 577 consecutive infants with malformations of unknown cause and reported that GDM was a significant risk factor for holoprosencephaly, upper/lower spine/rib anomalies, and renal and urinary system anomalies. However, owing to the heterogeneous nature of GDM, which includes previously unrecognized and newly diagnosed Type 2 diabetes, they could not rule out the

possibility that the teratogenic effect is related to latent Type 2 diabetes. Nevertheless, they concluded that pregnancies complicated by GDM should be considered at risk of congenital anomalies. By contrast, another population-based retrospective study [64] showed that the rate of congenital malformations in the GDM group was only slightly higher than in the control group (OR = 1.3; 95% CI 1.0, 1.6). Interestingly, recent epidemiological data relate maternal obesity per se to congenital malformations; Mikhail et al. [65] found that compared with non-obese, non-diabetic African American women, obese non-diabetic African-American women were significantly more likely to have babies with a cardiac anomaly (OR 6.5, 95% CI 1.2, 34.9). Similarly, Watkins and Botto [66] reported that after excluding diabetic mothers and adjusting for potential confounders, overweight women were more likely than average-weight women to have a child with a major isolated heart defect. However, in a large prospective cohort study [67] of 22 951 pregnant women, obese women had no higher risk, overall, of having an offspring with a major defect. Their offspring, nevertheless, did have higher prevalence of minor defects. Another prospective case–control study of 20 248 newborns born in the city of Mainz [68] revealed that the prevalence of major malformations in children of obese mothers was higher than those of the total population (11.1% vs. 4%, OR 1.3, 95% CI 1.0, 1.7).

GDM and hypertensive disorders

Preeclampsia and gestational hypertension are apparently more frequent in women with GDM. A large study by Xiong et al. [69] detected preeclampsia in 2.7% of 2755 patients with GDM compared with only 1.1% of 108 664 patients with normal pregnancy (adjusted OR = 1.3; 95% CI 1.20, 1.41). Similar results were observed for gestational hypertension. Likewise, Dukler et al. [70] studied 380 primiparous women with preeclampsia and 385 primiparous control women for a total of 1207 and 1293 deliveries, respectively. After adjustment for confounding variables, GDM was strongly associated with the recurrence of preeclampsia in the second pregnancy (OR = 3.72; 95% CI 1.45, 9.53). Conditions associated with increased insulin resistance, such as GDM, PCOS, and obesity, may predispose patients to essential hypertension, hypertensive pregnancy, hyperinsulinemia, hyperlipidaemia, and high levels of plasminogen activator inhibitor-1, leptin, and tumour necrosis factor alpha. These findings may also be associated with a possible increased risk of cardiovascular complications [38]. Joffe et al. [44] provided further support for the role of insulin resistance in the pathogenesis of hypertensive disorders of pregnancy. In a prospective study of 4589 healthy nulliparous women, they found that the women with GDM had an increased relative risk of preeclampsia and all hypertensive disorders (RR = 1.67; 95% CI 0.92, 3.05 and RR = 1.54; 95% CI 1.28, 2.11, respectively). Risk ratios were not substantially reduced after further adjustment for ethnicity and BMI (OR = 1.41 and 1.48, respectively). Furthermore, even within the normal range, multivariate analysis demonstrated that the level of plasma glucose 1 h after a 50-g oral glucose challenge was an important predictor of preeclampsia. Innes et al. [60] evaluated 54 normotensive women who developed hypertension in pregnancy, and 51 controls with normotensive pregnancies, matched for parity. After adjustment for potential confounders, 2-h postload glucose levels remained strongly related to risk for hypertension and to peak mean arterial blood pressure, as did total glucose area under the curve.

Diagnosis

Non stress test

Amniotic fluid index

In the hypoxemic fetus, cardiac output is redirected to the brain, heart, and adrenals and away from less vital organs, such as the kidney; The reduction in renal perfusion leads to decreased fetal urine production, which may result in decreased amniotic fluid volume (oligohydramnios) over time.

Sonographic determination of the single deepest amniotic fluid pocket (SDP) Four quadran Amniotic Fluid İndex (AFI). The SDP and the amniotic fluid index (AFI) method are equivalent in their prediction of adverse outcome in singleton pregnancies

Interpretation of Single deepest pocket technique Oligohydramnios – depth <2 cm Normal – depth ≥2 cm and <8 cm Polyhydramnios – depth ≥8 cm

AFI measurement is calculated by first dividing the uterus into four quadrants using the linea nigra for the right and left divisions and the Oligohydramnios – AFI ≤5 cm Normal – AFI >5 cm and <24 cm Polyhydramnios – AFI ≥24 cm

Premature Birth and Its Prevention

If a baby is born before 37 weeks of gestation, they are considered premature. Premature babies (also called “preemies”) are at a higher risk of medical issues because their organs are underdeveloped and easily damaged by birth injuries or complications in early infancy (1).

Every year, 15 million babies are born preterm (2). Premature birth is often preventable – doctors can prolong a pregnancy to the proper time using the hormone progesterone or a procedure called cervical cerclage if they promptly diagnose issues that are risk factors for premature birth. Once these factors are diagnosed, physicians must tailor a customized health plan to help maintain the pregnancy and protect the health of both mother and baby. This plan varies greatly from case to case, given the wide variety of factors that can cause premature birth.

Complications of premature birth

When a baby is born preterm, they are not yet fully developed, which can predispose them to injuries (3). Some of the complications of premature birth include:

Under-developed lungs

Babies born preterm face complications involving the lungs because their lungs are one of the last things to develop in the womb (5). A doctor can check the maturity of the lungs while the baby is in the womb with a process called amniocentesis (6). This is when amniotic fluid is removed from the uterus for testing. In certain cases, a steroid injection of betamethasone can be given to the mother of a premature baby to speed up the maturity of their lungs.

Often the lungs of preemies cannot produce enough surfactant on their own yet, and surfactant is one of the key chemical compounds that help the lungs function and stay flexible and pliant (3). Without surfactant, the lungs stay stiff, which means they cannot expand and contract well enough to get the air they need. Because of this, preterm babies often need extra help breathing. Medical practitioners can provide surfactant to keep the lungs flexible. They can also help the baby's breathing with methods like positive-pressure ventilation, or in some cases where both the baby's heart and lungs need support, with extracorporeal membrane oxygenation (ECMO).

Other possible complications of premature birth include (3,4):

- **Heart Problems**: Premature babies commonly experience heart problems such as hypotension (low blood pressure) and patent ductus arteriosus (PDA).
- **Temperature control problems**: Premature babies don't have the stored body fat of full-term infants and often can't generate enough heat to restore what is lost. They can develop hypothermia.
- **Brain problems:** Premature babies are at greater risk of intraventricular haemorrhage and a variety of other brain injuries.
- **Immune system problems:** Premature babies have an underdeveloped immune system, which puts them at a higher risk of infection.
- **Blood issues:** Premature babies are at a higher risk of jaundice, anemia, and other blood issues.
- **Metabolism issues:** Premature babies often develop metabolism issues like hypoglycemia (low blood sugar).
- **Gastrointestinal issues:** The immature gastrointestinal systems of premature babies puts them at risk of many issues involving feeding.

Additionally, there are long-term conditions that are associated with premature birth. For more details, see our section "What kinds of conditions are associated with preterm birth?"

fetal macrosomia defined?

Macrosomia, also known as large for gestational age (LGA), can be defined as a condition in which a fetus or newborn weighs more than 4,000 grams at term, although some experts use a threshold of 4,500 grams. Researchers have suggested the following grading system, which may be useful for making decisions regarding method of delivery, such as whether to use forceps or vacuum extractors, or whether to perform a C-section (1):

- Macrosomia grade 1: 4,000 – 4,499 grams
- Macrosomia grade 2: 4,500 – 4,999 grams
- Macrosomia grade 3: over 5,000 grams (2)

Premature infants may be considered macrosomic if their weight exceeds the 90th percentile for gestational age, although some researchers have suggested a more stringent approach (95th percentile or even 97.75th percentile) (1).

How common is fetal macrosomia?

In the United States, approximately 8 percent of term babies have macrosomia grade 1, and 1.1 percent have macrosomia grade 2. The prevalence of macrosomia varies greatly by country (1).

Causes of fetal macrosomia

Maternal and fetal hyperglycemia (high blood sugar) is thought to be a major cause of fetal macrosomia. The baby responds to this excess sugar by releasing insulin, insulin-like growth factors, and growth hormones, which increases fat deposition and fetal size.

Macrosomia often occurs when the mother is obese or has diabetes, particularly gestational diabetes (1). In some instances, macrosomia can also be caused by fetal medical conditions or genetic factors (3).

Risk factors for fetal macrosomia

There are many factors that increase the risk of macrosomia. When any of these risks are present, the physician should closely monitor the mother and baby for macrosomia and its potential complications. Risk factors for macrosomia include the following:

- **Maternal diabetes:** Both gestational and pre-gestational diabetes can cause the baby to grow very large.
- **Maternal obesity:** If a mother is obese or gains excessive weight during pregnancy, macrosomia is more likely.
- **Prior delivery of a macrosomic baby:** In one study, infants with grade 2 macrosomia were seven times more likely to have a subsequent macrosomic sibling (4).
- **Multiparity:** Women who have previously given birth (i.e. are "multiparous") are at higher risk for having a baby with fetal macrosomia. Grand multiparas may be at especially high risk (5).
- **Post-term pregnancy:** Pregnancies that go beyond 40 weeks have an increased incidence of macrosomia (1).
- **Advanced maternal age:** Women older than 35 years are more likely to have a baby diagnosed with macrosomia (3).
- **A male baby:** Male fetuses and infants tend to weigh more than females (1). Most babies who weigh more than 4,500 grams are male (6).
- **Ethnic background:** African American and Hispanic babies are at higher risk for macrosomia (1).
- **Genetic factors:** Taller, heavier parents may be more likely to have larger babies (6). Genetic abnormalities such as Pallister-Killian syndrome and Beckwith-Wiedemann syndrome also increase the risk of macrosomia (1).
- **Congenital anomalies:** Certain congenital anomalies, such as ventricular septal defects and atrial septal defects, are associated with macrosomia (7).

Diagnostic procedures and signs of fetal macrosomia

Macrosomia should be suspected if major risk factors (such as maternal obesity or diabetes) are present. In addition to asking about your medical history, doctors can assess the baby's size using the following methods (1, 3):

- **Ultrasound:** Ultrasound technology is the most accurate method used to estimate fetal size. Hadlock's formula (which takes into account head circumference, abdominal circumference, and femur length) is thought to be the most accurate sonographic method for estimating fetal weight.
- **Fundal height measurement:** The fundal height refers to the length from a woman's pubic bone to the top of her uterus. A higher than normal fundal height could indicate macrosomia.
- **Palpation of the maternal abdomen:** Physicians can estimate fetal weight by palpating the mother's abdomen (a common method is called the "Leopold maneuver").
- **Checking amniotic fluid level:** An excess of amniotic fluid (polyhydramnios) can be indicative of macrosomia because larger babies produce more urine (late in pregnancy, the amniotic fluid is made up primarily of fetal urine).
- **Nonstress test:** This records the baby's heart rate when they move. Abnormal results of a nonstress test should be taken as a warning sign that something may be wrong with the pregnancy or the baby.
- **A biophysical profile (BPP):** This uses the nonstress test in conjunction with ultrasound to check the baby's movements, heart rate, and level of amniotic fluid.

If macrosomia is suspected, physicians should recommend frequent prenatal testing in order to assess fetal well being and determine whether medical intervention is necessary.

Preventing and managing fetal macrosomia

Doctors should advise obese and diabetic women to take certain precautions before attempting to become pregnant, in order to avoid fetal macrosomia and other complications. Pre-pregnancy weight loss can reduce the risk of macrosomia in obese women, and is a very important intervention because it is generally not safe to lose a substantial amount of weight *during* pregnancy. Management of diabetes before and during pregnancy can also reduce the likelihood of macrosomia (1). General practitioners should refer obese and diabetic women to maternal-fetal specialists who can help them achieve health goals.

If the physician suspects macrosomia, a vaginal delivery still may be occasionally attempted, but only with the informed consent of the mother. More typically, cesarean section is recommended for suspected macrosomia. There are a variety of risks associated with vaginal delivery of a macrosomic baby, including shoulder dystocia (a complication in which the baby's shoulder gets stuck behind the mother's pelvic bone), birth trauma, and HIE. Use of Instruments such as forceps and vacuum extractors is associated with a 50% chance of shoulder dystocia in deliveries involving macrosomia (and in general, these instruments increase the risk of shoulder dystocia) (6). If doctors apply excessive force to deliver a baby with shoulder dystocia, this can lead to brachial plexus injury and other forms of damage. Thus, risk factors for shoulder dystocia should

be carefully reviewed prior to utilization of forceps and vacuum extractors. Physicians should try and avoid the procedure if substantial risk appears to be present.

If the pregnancy is allowed to run its course, or if induction is attempted, the physician should be prepared to deliver by C-section in the event of an emergency. In addition to shoulder dystocia, deliveries involving macrosomia are at higher risk for prolonged/arrested labor and birth asphyxia (3), among other issues (see next section).

Early/near-term induction of labor with drugs such as Pitocin (synthetic oxytocin) could theoretically reduce complications associated with macrosomia (since the baby will be slightly smaller when delivered), but some studies have found that labor induction does not reduce the risk of complications associated with macrosomia, and might increase the need for a C-section (8). More recent studies have found some purported benefits, but the American College of Obstetrics and Gynecologists (ACOG) still recommends against induction of labor in cases involving large for gestational age babies.

According to ACOG, If the mother has diabetes and the baby likely weighs more than 4,500 grams, a C-section may be the safest method of delivery. A C-section will also likely be recommended if the baby weighs 5,000 grams or more, even if the mother does not have diabetes (6).

After delivery, the baby will likely be examined for signs of birth injuries, abnormally low blood sugar (hypoglycemia), and a blood disorder that affects the red blood cell count (polycythemia) (9).

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- Complications
- Why is Preventing Preterm Birth so Important?
- Conditions Associated with Preterm Birth
- Preventing Preterm Birth
- Reducing the Risk of Injury in Preterm Babies

Complications of premature birth

When a baby is born preterm, they are not yet fully developed, which can predispose them to injuries (3). Some of the complications of premature birth include:

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Often the lungs of preemies cannot produce enough surfactant on their own yet, and surfactant is one of the key chemical compounds that help the lungs function and stay flexible and pliant (3). Without surfactant, the lungs stay stiff, which means they cannot expand and contract well enough to get the air they need. Because of this, preterm babies often need extra help breathing. Medical practitioners can provide surfactant to keep the lungs flexible. They can also help the baby's breathing with methods like positive-pressure ventilation, or in some cases where both the baby's heart and lungs need support, with extracorporeal membrane oxygenation (ECMO).

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Additionally, there are long-term conditions that are associated with premature birth. For more details, see our section "What kinds of conditions are associated with preterm birth?"

Breathing support: risk of overventilation and hypocarbia

One problem that can occur in babies born preterm is brain injury stemming from overventilation and hypocarbia. The human body's regulatory mechanisms operate under specific ratios of CO2 and oxygen in the blood. If a baby is ventilated at too high a setting, the amount of CO2 in their

blood can drop below a safe level. This is known as **hypocarbia**. If hypocarbia continues for too long, this can cause brain injuries like periventricular leukomalacia (PVL), among others. If a baby is over-ventilated, the pressure from the machine can also cause lung damage like bronchopulmonary dysplasia (BPD) and pneumothorax (when the baby's lung collapses). This can cause long-term scarring in the lungs and can compromise how well oxygen is delivered to the baby's brain and other organs.

preventing preterm birth so important

With proper support, babies delivered at 28 weeks or later usually do very well, and develop without long-term problems. Each additional week of gestation and 100-gram increase in birth weight (in the lower-to-mid ranges of gestational age and birth weight) greatly reduces mortality risk. **The longer a baby gestates, the less likely it is they will have a prematurity-related injury (7).**

There are ways that medical practitioners can decrease the risk of preterm birth, especially when analyzing a mother's prior health history closely.

kinds of conditions are associated with preterm birth?

Possible long-term complications of premature birth include (5):

- **Cerebral palsy:** Premature babies are more susceptible the brain injuries, infection, and blood flow issues that bring about cerebral palsy, a movement disorder that affects muscle tone, movement, balance, and coordination.
- **Hypoxic-ischemic encephalopathy (HIE):** Some of the short-term complications of premature birth can lead to HIE, a neonatal brain injury caused by oxygen deprivation and/or limited blood flow to the brain at or near the time of birth.
- **Developmental disabilities**: Some of the short-term complications of premature birth can lead to developmental disabilities including cognitive and behavioural issues.

Fetal complications and birth injuries associated with macrosomia

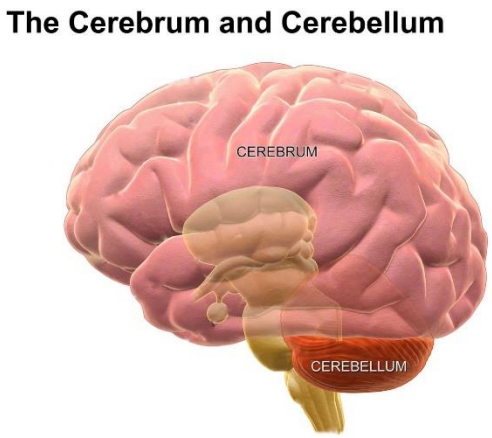
The following are just a few examples of complications and birth injuries that a macrosomia baby may experience.

- **Injuries from forceps and vacuum extractors:** Excessive force from inappropriate use of these instruments can cause trauma and conditions such as brachial plexus injuries, intracranial hemorrhages (brain bleeds), seizures, and cerebral palsy.
- **C-section:** Macrosomia increases the likelihood that a C-section (planned or emergent) will be necessary. If a baby becomes lodged in the birth canal, it is very important to get them out quickly. Delaying a C-section can result in permanent brain damage. The medical team must be well prepared for this possibility.
- **Hypoxic-ischemic encephalopathy (HIE):** This is a type of brain injury in which a baby is severely deprived of oxygen, resulting in cell death and, often, permanent conditions

such as cerebral palsy, seizures, and learning disabilities. This happens many times when the baby is too big to fit through the birth canal and gets stuck or if the umbilical cord becomes compressed.

- **Uterine rupture:** If a mother had a prior C-section or major uterine surgery, macrosomia increases the risk of uterine rupture (3), a serious complication in which the uterus tears open along the surgical scar line. Indeed, prior uterine surgery can increase the risk of uterine rupture even in the absence of macrosomia. Uterine rupture can cause serious problems such as HIE, and puts the lives of both the mother and baby in danger.

Cerebral palsy (CP) is caused by damage or abnormalities in the part of the brain that controls movement. It is considered a motor disorder, meaning that it's characterized by unusual or involuntary movements. Cerebral palsy also often causes musculoskeletal conditions that manifest in joint and bone deformities. Additionally, many people with cerebral palsy have issues such as epilepsy, cognitive impairments, and problems with vision or hearing. **Cerebral palsy is the most common motor disability in childhood**, affecting one in 323 children (1). A large number of diagnoses are caused by preventable birth injuries and medical malpractice.



What is cerebral palsy?

Cerebral palsy (CP) is a group of non-progressive motor conditions that cause physical disability. CP is caused by damage to the motor control centers of the developing brain, which can occur before a baby is born, during childbirth, or after birth up to age five (2). 'Cerebral' refers to the cerebrum, which is the affected area of the brain (although the disorder may involve other parts of the brain, such as the cerebellum), and 'palsy' refers to a disorder of movement (3).

The effects of cerebral palsy can vary dramatically from one individual to the next. Some have only minor impairments and are totally independent; others struggle greatly with the tasks of daily life and require extensive assistance and 24-hour care.

Currently, cerebral palsy has no cure, but there are a variety of treatments and therapies that can alleviate certain symptoms and improve function.

A cesarean delivery — also known as a C-section or cesarean section — is the surgical delivery of a baby. It involves one incision in the mother's abdomen and another in the uterus.

It's a common procedure that's used to deliver nearly one-third of babies in the United States, according to the Centers for Disease Control and Prevention Trusted Source.

Cesarean deliveries are generally avoided before 39 weeks of pregnancy so the child has proper time to develop in the womb. Sometimes, however, complications arise and a cesarean delivery must be performed prior to 39 weeks.

Why a cesarean delivery is done

A cesarean delivery is typically performed when complications from pregnancy make traditional vaginal birth difficult, or put the mother or child at risk.

Sometimes cesarean deliveries are planned early in the pregnancy, but they're most often performed when complications arise during labor.

Reasons for a cesarean delivery include:

- baby has developmental conditions
- baby's head is too big for the birth canal
- the baby is coming out feet first (breech birth)
- early pregnancy complications
- mother's health problems, such as high blood pressure or unstable heart disease
- mother has active genital herpes that could be transmitted to the baby
- previous cesarean delivery
- problems with the placenta, such as placental abruption or placenta previa
- problems with the umbilical cord
- reduced oxygen supply to the baby
- stalled labor
- the baby is coming out shoulder first (transverse labor)

The risks of a cesarean delivery

A cesarean delivery is becoming a more common delivery type worldwide Trusted Source, but it's still a major surgery that carries risks for both mother and child. Vaginal birth remains the preferred method for the lowest risk of complications. The risks of a cesarean delivery include:

- bleeding
- blood clots
- breathing problems for the child, especially if done before 39 weeks of pregnancy
- increased risks for future pregnancies
- infection
- injury to the child during surgery
- longer recovery time compared with vaginal birth
- surgical injury to other organs

- adhesions, hernia, and other complications of abdominal surgery.

Management of Gestational Diabetes BLOOD GLUCOSE MONITORING In patients requiring insulin therapy, the ideal frequency of glucose monitoring has not been established. A common practice is to check the glucose level four times daily. A first morning glucose level can rule out fasting hyperglycemia, and additional one- or two-hour postprandial values can ensure adequate control. Postprandial testing is preferable to preprandial testing. In one randomized study comparing postprandial and preprandial blood glucose monitoring in patients with gestational diabetes who required insulin therapy, those who measured their glucose levels after meals had larger drops in A1c (−3.0 versus −0.6 percent, P betes who were randomly assigned to receive primary dietary therapy or no specific treatment. The review concluded that insufficient evidence exists to recommend dietary therapy in patients with altered glucose metabolism. The ideal diet for women with gestational diabetes remains to be defined, and current recommendations are based on expert opinion.14 The ADA recommends nutrition counseling (with a registered dietitian, if possible) and a diet that adequately meets the needs of pregnancy but restricts carbohydrates to 35 to 40 percent of daily calories. Caloric restriction should be approached with caution, because two studies have reported a relationship between elevated maternal serum ketone levels and reduced psychomotor development and IQ at three to nine years of age in the offspring of mothers with gestational diabetes.21,22 For patients with a body mass index greater than 30 kg per m2 , the ADA suggests lowering daily caloric intake by 30 to 33 percent (to approximately 25 kcal per kg of actual weight per day), which avoids ketonemia. Regular exercise has been shown to improve glycemic control in women with gestational diabetes, but it has not been shown to affect perinatal outcomes.23 (For additional dietary recommendations, see the accompanying patient information handout.) INSULIN Most,24-26 but not all,27,28 prospective trials involving insulin therapy in women with gestational diabetes have shown a reduction in the incidence of neonatal macrosomia. Therefore, insulin therapy traditionally has been started when capillary blood glucose levels exceed 105 mg per dL (5.8 mmol per L) in the fasting state and 120 mg per dL (6.7 mmol per L) two hours after meals. These cutoff values are derived from guidelines for managing insulin in pregnant women who have type 1 diabetes. A more aggressive goal of a fasting capillary blood glucose level below 95 mg per dL (5.3 mmol per L) is supported by a prospective study of 471 women with gestational diabetes that showed a decrease in large-for-gestational-age neonates, from 28.6 to 10.3 percent (relative risk, 5.99; 95 percent confidence interval, 1.37 to 8.88), in the women with fasting blood glucose levels of 95 to 105 mg per dL who were treated, respectively, with diet or insulin; the study reported no data on additional birth outcomes.29 [Evidence level B, nonrandomized observational study] This more conservative goal is recommended in the most recent ACOG practice bulletin on gestational diabetes.15 Because of variable and imperfect data on this point, it is acceptable to use either cutoff value for fasting glucose testing. One prospective nonrandomized study of 445 patients has shown a reduction in operative deliveries and birth trauma in women with gestational diabetes who are treated with insulin.30 However, the findings of this study remain to be demonstrated in an adequately powered RCT. There are no specific studies declaring one type of insulin or a certain regimen as superior in affecting any perinatal outcome. A common initial dosage is 0.7 units per kg per day, with one dose consisting of two thirds of the total amount given in the morning and one dose consisting of one third of the total amount given in the evening. One third of each dose is given as regular insulin, and the remaining two thirds as NPH insulin. A recent study of 42 women with gestational diabetes supports the safety of very-short-acting insulin lispro, which can be used with once-daily extended insulin ultralente.31 The simplest regimen that will control blood glucose levels is the best. Physicians should expect to increase the insulin dosage as the pregnancy progresses and insulin resistance increases. No published guidelines are available to help family physicians treat patients with gestational diabetes who require insulin. When necessary, collaborative care with an obstetrician or perinatologist is advisable. ORAL HYPOGLYCEMIC MEDICATIONS Use of oral hypoglycemic agents to treat gestational diabetes has not been recommended because of concerns about potential teratogenicity and transport of glucose across the placenta (causing prolonged neonatal hypoglycemia).32 Although first-generation hypoglycemic agents (chlorpropamide [Diabinese], tolbutamide [Orinase]) have been shown to cross the placenta, recent in vitro and in vivo evidence has determined that glyburide (Micronase) does not enter the fetal circulation.33,34 A recent RCT comparing the use of glyburide and insulin in women with gestational diabetes demonstrated that glyburide therapy resulted in comparable maternal outcomes (e.g., glycemic control, cesarean deliveries) and neonatal outcomes (e.g., macrosomia, hypoglycemia, intensive care unit admissions). Glyburide therapy was not started before 11 weeks of gestation and was not detected in any of the neonatal cord blood samples. Preliminary evidence from this trial suggests that glyburide may be a safe, effective alternative to insulin in the management of gestational diabetes. The ACOG15 and the ADA20 agree that glyburide should not be prescribed for the treatment of gestational diabetes until additional RCTs support its safety and effectiveness. Despite these recommendations, many physicians are using glyburide in this setting because of its ease of use compared with insulin. In a recent prospective cohort study of patients with polycystic ovary syndrome,33 metformin therapy has been shown to decrease the subsequent incidence of gestational diabetes, reduce first-trimester miscarriage

rates, and result in no apparent increase in congenital anomalies.35 RCTs are needed to demonstrate the safety and effectiveness of metformin (Glucophage) in pregnancy before use of this medication is warranted for the treatment of gestational diabetes. ANTEPARTUM FETAL ASSESSMENT Data on gestational diabetes and an increased risk of fetal demise are conflicting. The 2001 ACOG practice bulletin15 concludes that evidence is insufficient to determine the optimal antepartum testing regimen in women with gestational diabetes who have relatively normal glucose levels on diet therapy and no other perinatal risk factors. Acceptable practice patterns for monitoring pregnancies complicated by gestational diabetes range from testing all women beginning at 32 weeks of gestation to no testing until 40 weeks of gestation. The ACOG15 recommends antenatal testing for patients whose blood glucose levels are not well controlled, who require insulin therapy, or who have concomitant hypertension. The antenatal testing can be initiated at 32 weeks of gestation. In this situation, no method of antenatal testing has proved superior to others. Community preference may dictate use of the nonstress test, the modified biophysical profile (i.e., nonstress test and amniotic fluid index), or a full biophysical profile. TIMING AND ROUTE OF DELIVERY In gestational diabetes, shoulder dystocia is the complication most anticipated at the time of delivery. In one study,36 this complication occurred in 31 percent of neonates weighing more than 4,000 g who were delivered vaginally to unclassified mothers with diabetes. No prospective data support the use of cesarean delivery to avoid birth trauma in women who have gestational diabetes. One remaining limiting factor is the 13 percent error rate (± 2 SD) in estimating fetal weight by ultrasonography.37 A decision analysis38 that evaluated the cost and efficacy of a policy of elective cesarean delivery for an estimated fetal weight of 4,500 g (9 lb, 15 oz) in mothers with diabetes found that 443 cesarean deliveries would need to be performed to prevent one case of brachial plexus injury, at a cost of $930,000. A reasonable approach is to offer elective cesarean delivery to the patient with gestational diabetes and an estimated fetal weight of 4,500 g or more, based on the patient's history and pelvimetry, and the patient and physician's discussion about the risks and benefits. There are no indications to pursue delivery before 40 weeks of gestation in patients with good glycemic control unless other maternal or fetal indications are present. INTRAPARTUM MANAGEMENT The goal of intrapartum management is to maintain normoglycemia in an effort to prevent neonatal hypoglycemia. Patients with diet-controlled diabetes will not require intrapartum insulin and simply may need to have their glucose level checked on admission for labor and delivery. While patients with insulin-requiring diabetes are in active labor, capillary blood glucose levels should be monitored hourly. Target values are 80 to 110 mg per dL (4.4 to 6.1 mmol per L).39 POSTPARTUM MANAGEMENT Women with gestational diabetes rarely require insulin in the postpartum period.As insulin resistance quickly resolves, so does the need for insulin. Patients with diet-controlled diabetes do not need to have their glucose levels checked after delivery. In patients who required insulin therapy during pregnancy, it is reasonable to check fasting and two-hour postprandial glucose levels before hospital discharge. Because women with gestational diabetes are at high risk for developing type 2 diabetes in the future, they should be tested for diabetes six weeks after delivery via fasting blood glucose measurements on two occasions or a two-hour oral 75-g glucose tolerance test. Normal values for a two-hour glucose tolerance test are less than 140 mg per dL. Values between 140 and 200 mg per dL (11.1 mmol per L) represent impaired glucose tolerance, and greater than 200 mg per dL are diagnostic of diabetes. Screening for diabetes should be repeated annually thereafter, especially in patients who had elevated fasting blood glucose levels during pregnancy.40 Breastfeeding improves glycemic control and should be encouraged in women who had gestational diabetes.41 Contraception should be discussed, because women who have diabetes during one pregnancy are likely to have the same condition in a subsequent pregnancy. There are no limits on the use of hormonal contraception in patients with a history of gestational diabetes. As previously noted, these women also are at increased risk of developing type 2 diabetes in the future. Patients should be counseled about diet and exercise. By losing weight and exercising, women can significantly decrease their risk of developing diabetes.

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