

## **Gestational Diabetes Mellitus Health Assessment: Distinct Pattern of Overgrowth, Macrosomia Fetuses Features, and its Management**

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### **Abstract**

Fetal macrosomia, defined as a birth weight of fewer than 4,000 grams, affects 12% of normal-weight babies and 15–45% of babies born to women with gestational diabetes (GDM). Macrosomia is more likely to occur in pregnant diabetic women because of increased insulin resistance. A greater volume of glucose from the mother's blood enters the womb of the fetus in gestational diabetes mellitus (GDM). As a result, the fetus's glucose is stored as body fat, resulting in macrosomia, frequently referred to as "large for gestational age." This article summarizes research literature on the implications of gestational diabetes mellitus and features of fetal macrosomia. Additionally, the impact of macrosomia-related comorbidities on delivery outcomes will be explored to prioritize health assessment for both mother and baby. If undiagnosed and not addressed in time, fetal macrosomia is a typical adverse neonatal result of GDM. Macrosomia raises the risk of shoulder dystocia, clavicle fractures, and brachial plexus injury in infants and increases the rate of neonatal intensive care unit hospitalizations. The hazards linked with macrosomia for the mother include cesarean birth, postpartum hemorrhage, and vaginal lacerations. Infants born with GDM have a higher chance of being overweight or obese at a young age (during adolescence) and developing type II diabetes later in life. Epigenetic changes in a fetus's DNA when its mother has gestational diabetes are also a cause for concern because they could lead to GDM and type II diabetes transmission down the family tree. If you've ever wondered what causes gestational diabetes mellitus (GDM), macrosomia, and its management, this review will explore this context.

**Keywords:** Gestational diabetes Mellitus, Preterm, Macrosomia, postpartum hemorrhage, Prediabetic woman, epigenetics.

### **Introduction:**

GDM (gestational diabetes mellitus) is described as varying degrees of glucose intolerance that begins or is first recognized during pregnancy. Diabetic mothers are three times more likely to give birth to a baby with macrosomia than their nondiabetic counterparts [1]. Due to a lack of universally agreed-upon diagnostic criteria for gestational diabetes, hyperglycemia and adverse pregnancy outcome (HAPO) occur. Pregnancy outcomes such as big for gestational age, cesarean delivery, fetal insulin levels, and neonatal fat content are associated with graded increases in the values of 75-gm 2-hour oral glucose tolerance. Diagnosis of gestational diabetes adopts as follows: a. 75-gm 2-hour oral glucose tolerance test thresholds are met or exceeded: fasting 92 mg/dL, 1-hour 180 mg/dL, or 2 hours 153 mg/dL [2].

A three-fold greater risk rate is possible for the babies born to diabetic moms to be with macrosomia than non-diabetic mothers. Macrosomia is 4,000 grams of birth weight or above the 90th percentile for gestational age. A globally agreed definition for macrosomia is difficult to establish. However, "macrosomia" suggests growth beyond the absolute birth weight (historically 4,000 g or 4,500 g), independent of gestational age. [3]. Maternal obesity, unlike maternal hyperglycemia, has a significant and independent effect on fetal macrosomia [4]. Stillbirth, newborn mortality (mainly due to birth asphyxia), birth injury, neonatal asphyxia, meconium aspiration, and cesarean delivery were significantly increased in those with a birthweight of 4500-4999 gm, not with a birthweight of 3500-3999 gm. Sudden infant death syndrome (SIDS) was much more significant for babies born at or above 5000 gm [5]. Studies in numerous countries, including the developed countries have suggested that gestational diabetes mellitus is a high-risk factor for developing type 2 diabetes [6,7]. Age at delivery, pre-pregnancy body mass index (BMI), weight gain during pregnancy, maternal height, hypertension, and cigarette smoking all play a vital role. Another study documented that when fat women's newborns were compared to normal-weight women's newborns, the risk of macrosomia was more than doubled in obese women's newborns [8].

Diabetes in Early Pregnancy Study found that fetal birth weight correlates better with postprandial blood sugar levels in the second and third trimesters than fasting or mean glucose levels [3]. According to statistics, when postprandial glucose levels are 120 mg/dl or less, around 20% of newborns are macrosomic, and when glucose

levels are as high as 160 mg/dl, macrosomia can reach up to 35%. Pregnant women with diabetes with macrosomic fetuses experience a distinct pattern of fat buildup in the fetus's central, subcutaneous, abdominal, and interscapular regions [9]. They have thicker upper-extremity skinfolds, more prominent shoulder and extremity circumferences, a lower head-to-shoulder ratio, and much higher body fat. Common injuries such as Erb's palsy, shoulder dystocia, and brachial plexus are more common though fetal head growth is not increased. Still, shoulder and abdominal circumference can be significantly increased. Skeletal growth, on the other hand, is mainly unaffected [10]. The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) found a link between maternal fasting hyperglycemia and the risk of shoulder dystocia, with a 1-mmol increase in fasting glucose resulting in a 2.09 relative risk for shoulder dystocia [11].

Macrosomia has been linked to high rates of neonatal morbidity [12]. Compared to newborns born to women without diabetes, oversized neonates have a 5-fold higher rate of severe hypoglycemia and a 2-fold higher rate of neonatal jaundice [13]. Furthermore, high prenatal insulin levels appear to have a role in triggering accelerated fetal growth. The larger, thicker babies from diabetic pregnancies were likewise hyper-insulinemic in a study comparing umbilical cord serum in diabetic moms and controls [14]. Women at high risk of GDM could be identified using fetal development determined by routine ultrasound scans performed a few weeks prior to the diagnosis [15].

### **Pathophysiology**

GDM's mechanics are still not fully understood. Insulin resistance and gestational diabetes mellitus (GDM) are caused by the flowing maternal and fetal-placental factors.

### **The Fetal-Placental Unit's Role in the Development of GDM**

During pregnancy, the placenta grows in size as the pregnancy proceeds. In the maternal circulation, pregnancy-related hormones such as estrogen, progesterone, cortisol, and placental lactogen rise, accompanied by an increase in insulin resistance [16,17]. This typically happens between the 20th and 24th weeks of pregnancy. The production of placental hormones ends as the mother goes through parturition and delivers the fetus, as does the disease of GDM, strongly suggesting that these hormones are the cause of GDM [18].

In the second half of pregnancy, human placental lactogen increases by ten. It promotes lipolysis, which increases free fatty acids, providing an alternative energy source for the mother and supplying glucose and amino acids to the fetus. As a result, the rise in free fatty acid levels obstructs the insulin-mediated entrance of glucose into cells. As a result, human placental lactogen is thought to be a potent insulin antagonist during pregnancy [19].

### **Adipose Tissue's Role in the Development of GDM**

Adipocytokines, such as leptin, adiponectin, tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6, are produced by adipose tissue, as are the newly identified resistin, visfatin, and apelin [20, 21]. The involvement of adipocytokines and higher lipid concentrations in pregnancy has been linked to changes in insulin sensitivity in both non-pregnant and pregnant women [22]. According to evidence, one or more adipokines may impede insulin signaling and produce insulin resistance [23]. TNF-alpha, in particular, has been linked to a decrease in insulin sensitivity [24].

### **Modified Hypothesis of Pedersen**

Over half a century ago, the Pedersen hypothesis was first proposed. Type-1 diabetic ladies were the primary focus of Jorgen Pedersen's practice. He hypothesized that more significant glucose transfer from the mother to the fetus stimulated the fetal beta cell to secrete insulin, resulting in macrosomia. Perinatal mortality and morbidity were reduced by optimal maternal glucose control. In contrast, maternal obesity, GDM, and type-2 diabetes have increased significantly during the following decades [25]. Biomarkers may be able to improve macrosomia prediction in the future. As a biological source of information, biomarkers offer a glimpse into the in-utero environment that may be contributing to the rapid fetal growth seen in some cases [8]. As a result, biomarkers may provide macrosomia prediction capacity by reflecting the probable proximal drivers of abnormal growth. There may be a biological relationship (biomarker) between maternal glucose metabolism/diabetes and maternal weight, which may reflect "proximal macrosomia determinants" (pre-pregnancy obesity and GWG). Fetal macrosomia has been linked to both "direct" and "indirect" pathways, but the exact processes by which these risk factors affect fetal growth are yet unknown [9].

Insulin action and effectiveness are directly linked to the direct route [26]. When a mother has diabetes and obesity, the insulin resistance during pregnancy is magnified, leading to maternal hyperglycemia and abnormal cholesterol levels. According to the modified Pedersen hypothesis, poor of diabetic mother's control will lead to fetal adipocyte lipogenesis [27]. Glycosylated hemoglobin (HbA1c), glucose, and 1,5-anhydroglucitol are biomarkers of maternal glycemic management that may indicate the danger of the direct pathway (1,5-AG). Maternal triglycerides and cholesterol may mean Dyslipidemia-related growth consequences.

On the other hand, the placental function focuses on the indirect pathway (28). Feto-placental nutrition transport may be hampered by placental modifications connected to maternal diabetes and obesity, such as changes in structure, uteroplacental blood flow, and placental transporters (29). Fetal hyperinsulinemia is stimulated by this and the increased nutrients supply to the fetus.

According to Pedersen's theory of macrosomia's pathogenesis, maternal hyperglycemia produces fetal hyperinsulinemia. Hyperinsulinemia results in increased use of glucose and, thus, an enlarged adipose tissue. Hence, enlarged fetal adipose tissue can explain the pathophysiology of macrosomia. When maternal glycemic control is disturbed, the glucose crosses the placenta, and maternal serum glucose levels are high [28].

The maternally generated or exogenously injected insulin, on the other hand, does not cross the placenta. As a result, the fetal pancreas, capable of secreting insulin, begins to respond to hyperglycemia in the second trimester and produces insulin independently, regardless of glucose stimulation. Hyperinsulinemia (insulin is a primary anabolic hormone) combined with hyperglycemia (glucose is a significant anabolic fuel) causes an increase in the fetus' fat and protein storage, culminating in macrosomia [23].

### **Complications Associated with Macrosomia**

#### **Complications in Pregnancy**

Vaginal birth will be more complicated if the baby is a giant. There is a chance that the fetus will become blocked in the birth canal, that mechanical delivery (with forceps or suction) will be required, and that an unexpected or emergency cesarean section will be required. The danger of laceration and tear of the vaginal tissue during birth is more remarkable than when the infant is of standard size. A perineal tear can occur. There's also a reasonable probability you'll get uterine atony. Heavy bleeding and postpartum hemorrhage can occur if the uterus muscle fails to contract appropriately. In macrosomic births, the risk of postpartum hemorrhage and genital tract damage was 3–5 times higher [16]. Furthermore, if the mother has had a previous cesarean section, the risk of uterine rip along the previous scar line is increased.

#### **Fetal related complications**

##### **Immediate Consequences**

Preterm delivery risk occurs due to early labor induction before 39 weeks of pregnancy and premature rupture of membranes. Despite taking all required precautions before inducing early labor, neonates are still at risk of complications associated with prematurity, such as breathing and feeding difficulties, infection, jaundice, neonatal intensive care unit admission, and perinatal mortality. Related to birth trauma, Erb's Palsy with Shoulder Dystocia is one of the most severe consequences of vaginal delivery in macrosomic newborns. The risk of birth trauma is six times higher in newborns weighing 4,500 g or more [17], and the risk of brachial plexus injury is approximately 20 times higher when the birth weight is above 4,500 g [18].

##### **Birth Hypoglycemia**

The most common metabolic abnormalities in the neonate of a GDM mother are hypoglycemia. It occurs due to the fetus's hyperinsulinemia reaction to maternal hyperglycemia in gestation. Hypoglycemia can cause more significant issues, such as severe central nervous system and cardiac problems. The most potent long-term consequences are neurological impairment resulting in mental retardation, recurrent seizure activity, developmental delay, and personality disorders.

##### **Jaundice in newborns**

Prematurity reduced hepatic conjugation of bilirubin and increased enterohepatic circulation of bilirubin due to poor nutrition are all possible causes of jaundice. Neonates with macrosomia have a high oxygen demand, resulting in increased erythropoiesis and, eventually, polycythemia. As a result of the breakdown of these cells, bilirubin (a byproduct of red blood cells) levels rise, leading to newborn jaundice. Anomalies are present at birth. The most frequent congenital disabilities are heart defects and neural tube defects, such as spina bifida. Women with GDM have excessive blood sugar levels, which can harm the developing organs of the fetus, resulting in congenital abnormalities.

##### **Delayed Complications**

Childhood Obesity and Metabolic Syndrome are later complications. GDM has been implicated in much research as one of the causes of childhood obesity. Evidence-based reports of fetal programs of later obesity in offspring exposed to diabetes while still in the womb appear to be evidence-based. The kids of Primigravida Indian mothers with type II diabetes and GDM were larger for gestational age at birth and heavier than the offspring of prediabetic or nondiabetic women after roughly five years of age [30].

Exposure to maternal GDM was linked to a higher BMI, a larger waist, more visceral and subcutaneous adipose tissue, and a more centralized fat distribution pattern in 6- to 13-year-old multiethnic adolescents, according to the Exploring Perinatal Outcomes among Children (EPOCH) study. [20]. Furthermore, children exposed to maternal

GDM in utero had a more significant average BMI increase from 27 months to 13 years of age, as well as a higher BMI growth velocity from 10 to 13 years of age [21]

These data show that the long-term effects of in utero GDM exposure do not always manifest themselves in early childhood but rather during puberty, another vulnerable phase for obesity development. Offspring of diabetic mothers are more likely to develop metabolic syndromes, including high blood pressure, hyperglycemia, obesity, and abnormal cholesterol levels, raising the risk of heart disease, stroke, and diabetes.

#### **Epigenetics and GDM Transgenerational Transmission**

The aberrant metabolic intrauterine environment impacts the development of the fetus in GDM by triggering changes in gene expression through epigenetic mechanisms in vulnerable cells, eventually leading to diabetes in adulthood. GDM and other metabolic problems emerge in the offspring (F1 generation) of severely and mildly hyperglycemic mothers later in life, affecting the second generation (F2).

As a result, GDM causes a vicious cycle in which moms with GDM produce babies with epigenetic alterations who are more likely to suffer metabolic problems later in life, resulting in a new generation of mothers with GDM. Disease transfers from one generation to the next through epigenetic alterations. It is now commonly acknowledged that a poor pre-conceptional and intrauterine environment is linked to fetal metabolism epigenetic malprogramming and subsequent propensity to chronic, particularly metabolic diseases [22, 23].

The study of genetic changes in gene expression that occur without changes in the DNA sequence is known as epigenetics [24]. In mammalian cells, DNA methylation and histone modifications are two important epigenetic regulators that are functionally related in transcription and may provide a mechanism for steady gene activity propagation from one to the next generation [25]. The geographical, temporal, and parent-specific highly coordinated gene expression patterns are controlled by biochemical alterations, such as DNA methylation and histone modifications. Individuals' epigenetic diversity may be genetically or environmentally determined, as external factors can cause epigenetic alterations [26]. According to several studies, early unfavorable conditions have been linked to diabetes and metabolic dysfunction later in life. Although the processes underlying the epigenetic alterations that allow for transgenerational transfer are unknown, evidence shows that methylation in germ cells may be to blame [27]. Others have proposed that the hyperglycemic uterine environment during pregnancy impacts many loci in the fetal epigenome, causing metabolic programming and thus transgenerational transmission of GDM and other metabolic illnesses [28, 29].

In one study [30], the expression of imprinted genes *Igf2* and *H19* was downregulated in pancreatic islets in both F1 and F2 offspring of GDM mothers in a rat model, which was caused by the abnormal methylation status of the differentially methylated region, which could be one of the mechanisms for impaired islet ultrastructure and function. Additionally, changed *Igf2* and *H19* gene expression was discovered in sperm of adult F1 GDM children in the same study, demonstrating that epigenetic modifications in germ cells led to transgenerational transmission.

Cord blood and the placenta of mothers with GDM were investigated in another study [28] to see if GDM had any effect on the epigenome of the following generation. In GDM groups, the methylation levels of the maternally imprinted *MEST* gene, the nonimprinted glucocorticoid receptor *NR3C1* gene, and interspersed ALU repeats were considerably lower than in controls. In people with morbid obesity, blood *MEST* methylation was significantly lower than in normal-weight controls, suggesting that *MEST* epigenetic malprogramming may contribute to obesity risk throughout life.

To further understand the epigenetic mechanisms of GDM and transgenerational transformation, several research on various genes were conducted. These investigations discovered epigenetic changes in the genes under investigation [28]. As a result of these studies, we can deduce that epigenetic pathways predispose offspring to type 2 diabetes, GDM, and other metabolic illnesses later in life. The fetus requires increased insulin to deal with high glucose levels caused by GDM is an environmental factor that likely triggers epigenetic changes in the early stages of life, affecting genes involved in pancreatic development and B-cell function, peripheral glucose uptake, and insulin resistance.

#### **Obesity in mothers, gestational diabetes, and macrosomia**

The majority of moms with GDM are fat, and GDM affects a large percentage of obese women [35]. Compared to pregnant women of average weight, the risk of developing GDM was 2.14-fold higher in overweight pregnant women, 3.56-fold higher in obese pregnant women, and 8.56-fold higher in severely obese pregnant women. The prevalence of macrosomia was 6.7% among 17,244 non-obese women without GDM, compared to 10.2 percent in 2,791 non-obese women with GDM and 20.2% in 935 obese women with GDM, according to data from the HAPO (Hyperglycemia and Adverse Pregnancy Outcomes) research.

It has been discovered that maternal fat rather than high blood sugar during pregnancy is a more robust indicator of a large-for-gestational-age baby. In a trial, researchers found that newborn overweight frequency in gestational

diabetic mothers was 50% higher than in non-gestational diabetic mothers in both the non-obese and obese groups than non-GDM. Obesity was linked to a 2-fold increased risk of macrosomia in both the non-GDM and GDM groups. Solely 26% of people with GDM had macrosomia, 33% of people with GDM and obesity had macrosomia, and 41% of people with obesity only had macrosomia. According to a study in Spain, the most significant factor correlated with maternal BMI was 23% of big babies, while GDM was responsible for almost four percent [31]. Women who did not have GDM but were obese had a 13.6% higher risk of macrosomia (defined as a child weighing 4,000 g or more at birth) than women who did not have GDM.

We can deduct from this that, whereas mothers with diabetes and obese mothers are related to negative pregnancy outcomes, both have a higher impact on macrosomia.

### **Macrosomia Management**

A variety of treatment options for macrosomia depend on the study and range from expecting management to elective induction of labor before the due date to choosing cesarean birth with an estimated fetal weight >4,500 grams. Studies have demonstrated that spontaneous labor has a better chance of resulting in vaginal delivery than labor induction. However, natural childbirth is questionable to start with the limited choice due to gestational age. Maternal morbidity, neonatal morbidity, and death increase as the gestational week approaches forty-one weeks. As a result, prompt action to initiate delivery is required.

### **Early Labor Initiation and surgical methods**

Given that the fetus grows at a pace of 230 grams per week after 37 weeks of gestation, elective labor induction before or near term has been advocated to avoid macrosomia and its problems [44]. However, two conditions must be met to induce labor: the first is fetal lung maturation. The lung maturity of fetuses born to diabetic mothers has been delayed. Usually, pulmonary development occurs between 34 and 35 weeks of pregnancy. Ninety-nine percent of fetuses are matured by 37 weeks. The lung in a diabetic mother's fetus, on the other hand, may not grow until 38.5 weeks. Secondly, a ripe cervix with a Bishop score of 6 is required for the patient undergoing induction. Otherwise, there is a greater risk of induction failure and subsequent cesarean surgery. One study compared the results of a suspected big baby born to moms who had emergency pregnancy management versus elective labor induction. In individuals assigned to the electively induced group, the rate of cesarean sections was significantly high. According to the ACOG, people with gestational diabetes mellitus (GDM) who have well-controlled blood glucose measurements through food and exercise should not be induced into labor before 39 weeks. They propose expecting management for these women up to 40 weeks, six days [32]. Elective induction of labor for macrosomia has been shown in some trials to increase the cesarean delivery rate without improving outcomes during the perinatal period [33].

Many studies recommend that patients suspected of having a macrosomia baby, particularly mothers of diabetes, "insulin-dependent diabetes," and a previous history of overweight babies, have a cesarean section to avoid maternal and fetal delivery stress. Unfortunately, calculating the fetus's weight is inaccurate [34]. For women with gestational diabetes, elective induction at term is related to an increased chance of cesarean birth. According to one study, an elective cesarean delivery to avoid brachial injury is unjustified in the general population [35].

### **Neonatal Management**

A neonate who is too big for their gestational age is not merely a preterm or post-term newborn; it can also be a term or "preterm infant." This is important to remember because treatment management and major priorities may differ. Maternal blood sugar levels that are strictly controlled decrease the risk of perinatal complications. The diabetic pregnant women should have their newborns undergo a complete medical examination, with newborn congenital disabilities (congenital heart defects, fistula: tracheoesophageal, and abnormalities: central nervous system) and trauma of more significant concern at the birth. Pregnant women with GDM should have their blood sugar, polycystic ovarian syndrome, high levels of bilirubin, and electrolyte imbalances closely monitored for abnormalities. Within the first hour of life, the blood sugar needs to be measured, then every hour for the next 6–8 hours, and after that as needed. Newborns should be fed immediately with oral feeding, preferably breastfeeding, which should be initiated if feasible, and if insufficient, an intravenous glucose infusion should be created [11].

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