

# Maternal diabetes and neonatal outcome

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## ABSTRACT

Diabetes during pregnancy is more and more frequent worldwide because of the rising incidence of its known risk factors, such as high body mass index, sedentary lifestyle, and hypercaloric diets. It can be either a preexisting condition, or it can be first diagnosed during pregnancy, usually between the 24th and the 28th week of gestation, when it receives the name of gestational diabetes mellitus. Both preexisting diabetes mellitus and gestational diabetes mellitus may have severe maternal and newborn consequences, especially if there is insufficient control of the maternal glycemic levels and progression of diabetes complications, such as microvascular disease and nephropathy. Infants of diabetic mothers may experience excessive birth weight or, on the contrary, low birth weight, trauma at birth, cardiomyopathy, respiratory distress syndrome, hypoglycemia, hypocalcemia, jaundice, or polycythemia. This study's aim is to gather and synthesize available information about maternal diabetes and its impact on fetal development and newborn outcome.

**Keywords:** maternal diabetes, pregnancy, gestational diabetes mellitus, neonatal complications, perinatal outcome, diagnosis, treatment

## Abbreviations

DM – diabetes mellitus

GDM – gestational diabetes mellitus

BMI – body mass index

GWG – gestational weight gain

SGA – small for gestational age

LGA – large for gestational age

NPID – National Pregnancy in Diabetes

IADPSG – International Association of the Diabetes and Pregnancy Study Group

CTG – cardiotocography

IUGR – intrauterine growth restriction

## INTRODUCTION

Pregnancy may be complicated by the presence of diabetes mellitus (DM), be it a preexisting type I or type II diabetes or gestational diabetes. Regardless of the onset moment, diabetes during pregnancy, especially if it is poorly controlled, has significant consequences for both the mother and the offspring. Infection, polyhydramnios, early rupture of membranes, preterm birth, and hypertensive disorders are all risks for pregnant women with diabetes mellitus (1,2). In addition, if diabetes precedes pregnancy, associated complications, such as retinopathy, nephropathy, and neuropathy, may occur or progress (2). Fetal and neonatal risks include congenital abnormalities, excessive growth or, on the

contrary, growth restriction, intrauterine death, shoulder dystocia, respiratory distress and hypoxia at birth, hypoglycemia, jaundice, and cardiomyopathy (2,3,4).

The association between diabetes mellitus and pregnancy has a rising prevalence worldwide due to the increasing frequency of its known risk factors, such as obesity, hypercaloric diets, and sedentary lifestyle in the general population. Obesity in women of reproductive age has negative consequences on a variety of pregnancy outcomes, including the risk of gestational diabetes mellitus (GDM) (5). Women with a body mass index (BMI) greater than 30 kg/m<sup>2</sup> should gain between 5 and 9 kg during pregnancy, according to the 2009 Institute of Medicine guidelines. While there is evidence to

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support not exceeding these gestational weight gain (GWG) recommendations, the advice of a GWG of less than 5 kg is disputed due to an increased risk of small for gestational age (SGA) neonates (6,7,8). However, for women with a BMI greater than 35 kg/m<sup>2</sup>, a gestational weight change of -4.9 to +4.9 kg has been shown to minimize the number of large for gestational age (LGA) births without increasing the number of SGA births (6,8).

In 2015, approximately 200 million women were suffering from diabetes mellitus, and their number is expected to rise to 300 million by 2030 (9). According to the International Diabetes Federation, 16.2% of the women who gave birth in 2015 had a form of hyperglycemia during pregnancy. Hyperglycemia in pregnancy can be divided into three large categories: 85.1% gestational diabetes mellitus, 7.4% other forms of diabetes found in pregnancy, mostly type II diabetes, and 7.5% preexisting diabetes (9). The association between type I diabetes and pregnancy is less frequent, being thought that it complicates no more than 0.1-0.2% of all pregnancies (10).

## METHODS

The purpose of this study is to review the literature and to gather and synthesize available information about maternal diabetes and its impact on fetal development and newborn outcome. We have used keywords such as “diabetes”, “pregnancy” and “neonatal complications” and we have searched articles through PubMed, Cochrane Library, the World Health Organization (WHO), the American Diabetes Association, the American College of Obstetricians, and Gynecologists, and the Royal College of Obstetricians and Gynaecologists. We identified over 40 articles describing maternal preexisting or gestational diabetes and its impact on the offspring, and we summarised the information we found.

## PREEXISTING DIABETES IN PREGNANT WOMEN

Pregnant women with type 1 and type 2 diabetes have worse pregnancy outcomes than the general population, including a three- to a fourfold greater rate of perinatal mortality (11,12). Stillbirth rates in the UK National Pregnancy in Diabetes (NPID) 2015 audit were found to be lower than those reported in the Confidential Enquiry into Maternal and Child Health audit from 2002-2003, indicating that improvement is feasible and underlining the value of national audit programs (13). In the NPID audit, social poverty was still highly linked to poorer diabetes pregnancy outcomes (13).

Structured preconception care for women with pre-gestational diabetes lowers the incidence of significant fetal abnormalities and perinatal mortality

in those with type 1 and type 2 diabetes and is cost-effective, according to the existing data (14,15). Glycemic control optimization, assessment and management of diabetes complications, discontinuation of potentially dangerous medicines, and initiation of folic acid are all included in this care, which is provided by an experienced multidisciplinary team (6).

Despite a lack of data on the effects of maternal hypoglycemia on neonatal outcomes (16), the well-known adverse effects of maternal hyperglycemia must be evaluated against the considerable risk of hypoglycemia. For the prevention of pre-eclampsia, preterm birth, and LGA neonates, optimal control in the first and second trimesters is becoming evident (13,17). Individualized for safety, the American Diabetes Association and the UK National Institute for Health and Care Excellence glycemic control objectives for women with type 1 diabetes during early pregnancy (HbA1c 48 mmol/mol [6.5 percent]) appear to be reasonable (18,19). HbA1c levels of 42 mmol/mol (6.0 percent) in later pregnancy should be safely achieved without significant hypoglycemia in some women with type 1 diabetes and many women with type 2 diabetes, according to recent NPID audit results (13). Women must be actively involved in their glycemic management through diabetes education, promotion of a healthy lifestyle, frequent blood glucose self-monitoring, and a supported active approach to insulin adjustment (6).

While insulin analogs, such as lispro, aspart, glargine, and detemir, have been linked to lower hypoglycemia and glucose excursions, the safety and efficacy of newer insulin analogs and concentrated insulin preparations must be determined. Continuous subcutaneous insulin infusion has not been shown to improve pregnancy outcomes; hence its usage should be done on a case-by-case basis (20).

Pregnancies in women with pre-gestational diabetes are frequently affected by retinopathy, nephropathy, and neuropathy. Ischemic heart disease is a less frequent but potentially fatal condition. Diabetes problems can show or progress at any moment during pregnancy; thus, screening is recommended before conception, during pregnancy, and after delivery (19,20). Diabetic nephropathy is linked to an increased risk of birth defects and preeclampsia (21,22). We would encourage researchers to look into early biochemical and clinical markers, as well as the use of low-dose aspirin, to prevent preeclampsia in diabetic women with and without nephropathy (23).

## GESTATIONAL DIABETES MELLITUS

In the United States, 2-5% of pregnancies are affected by GDM (24), which is a carbohydrate intoler-

**TABLE 1.** Therapeutic targets in pregnancy in women with preexisting type I and type II diabetes (23)

Fasting glucose	≤ 90 mg/dl
Premeal glucose	60-99 mg/dl
Postmeal glucose (at 1 hour)	≤ 130-140 mg/dl
Postmeal glucose (at 2 hours)	≤ 120 mg/dl
Mean glucose	≤ 100 mg/dl
Glucose in labor and during birth	80-110 mg/dl
HbA1c during pregnancy	6-6.5%

ance that develops or is first discovered during pregnancy (25). GDM-affected pregnancies are more likely to result in cesarean deliveries and labor anomalies, as well as unfavorable newborn outcomes such as macrosomia, hypoglycemia, still-birth, and neonatal intensive care unit admission (26,27).

It usually occurs between the 24th and 28th week of gestation and can affect all women, but there are some factors associated with a high risk of developing GDM (Table 2) (28).

**TABLE 2.** Risk factors for GDM

<ul style="list-style-type: none"> <li>• GDM in a previous pregnancy</li> <li>• A first-degree female relative who has had GDM</li> <li>• Age 40 years or over</li> <li>• Family history of type II diabetes</li> <li>• High body mass index</li> <li>• Previous episodes of high blood glucose levels</li> <li>• Polycystic ovary syndrome</li> <li>• Baby weighing 4,5 kg or more at previous birth</li> <li>• Antipsychotic or steroid medication</li> <li>• African, Middle Eastern or Hispanic nationalities</li> </ul>
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The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) tried to reach an international consensus on gestational diabetes screening and diagnosis by recommending a one-step 75 g oral glucose tolerance test at 24–28 weeks of pregnancy to all women who haven't been diagnosed with diabetes. When one or more threshold values are exceeded (fasting ≥ 92 mg/dl, 1-hour ≥ 180 mg/dl, 2-hour ≥ 153 mg/dl), diabetes is diagnosed (29,30).

For patients with GDM, current therapeutic approaches focus on maintaining euglycemia through a combination of diet and exercise. Insulin therapy is advised when diet and exercise fail to normalize blood glucose levels (27).

## NEONATAL OUTCOME

Infants of mothers with preexisting or gestational diabetes mellitus are at an increased risk of neonatal morbidities, such as congenital malformation, excessive fetal growth or growth restriction, still-birth, trauma at birth, respiratory distress, metabolic disorders, hypoxia, or cardiomyopathy (2).

According to the Pedersen theory, fetal macrosomia in diabetic women is linked to transplacental glucose transfer, which causes fetal hyperinsulinemia and, as a result, fetal overgrowth (31). In the HAPO trial, researchers discovered a linear and continuous association between infant body fat percentage, maternal glycemia, and fetal insulin levels as measured by cord C-peptide level (30,32). Boney et al. found that macrosomic offspring exposed to a diabetes-affected intrauterine environment have a higher risk of acquiring the metabolic syndrome in childhood and thus of developing type 2 diabetes mellitus later in life (33). As a result, newborn macrosomia in children of women with diabetes has the potential to perpetuate the vicious cycle of obesity, insulin resistance, and its repercussions in future generations (34).

There appears to be an increase in amniotic fluid insulin among pregnant diabetics with sub-optimal treatment, causing polyhydramnios and supporting the fetal hyperinsulinism idea. High amniotic fluid insulin levels are related to increased perinatal morbidity, according to various data (2).

Infants of women with diabetes are more likely to suffer delivery injuries, such as shoulder dystocia and brachial plexus trauma, and macrosomic fetuses are especially vulnerable (35). The extra fetal truncal fat accumulation in these pregnancies is most likely to blame. Once the birth weight exceeds 4 kg, there is a definite link between greater fetal size and the probability of shoulder dystocia (34,36). Shoulder dystocia occurs in 0.3-0.5 % of vaginal deliveries in healthy pregnant women, although it is 2- to 4-fold more common in diabetic women. Brachial plexus injury, facial nerve injury, and cephalohematoma are three common birth injuries linked to diabetes. The rate of birth defects is only slightly higher than the control when glycemic management was strictly observed (3.2 vs. 2.5%) (35).

It has been well documented that diabetic mothers' newborns may develop transient asymmetric septal hypertrophy. Cooper et al. discovered a link between maternal hyperglycemia in the third trimester of pregnancy and neonatal septal hypertrophy, macrosomia, and hypoglycemia (37). On the other hand, others suggested that strict maternal diabetes control did not rule out fetal cardiac growth acceleration (4,38). The majority of newborns with hypertrophic septal cardiomyopathy have no symptoms. However, if the obstruction is severe, patients may experience respiratory distress as well as other symptoms of heart failure (4).

Unless there is microvascular disease or hypertension, fetal surveillance methods such as cardiotocography (CTG), Doppler velocity waveforms of the umbilical artery, and fetal biophysical profile are less useful. Nephropathy and/or retinopathy are

the most common manifestations of microvascular illness during pregnancy (2). Reece et al. reviewed his own experience (27 patients with nephropathy) as well as the world literature at the time (39,40). Out of 315 women with diabetic nephropathy, 60% experienced hypertension by the third trimester, 41% pre-eclampsia, 15% intrauterine growth restriction (IUGR), 22% preterm birth, and 8% significant fetal abnormalities (2).

Fetal growth restriction not only increases the risk of short-term consequences, the most serious of which is intrauterine fetal death, but it also puts the child at risk for cardiovascular disease and types 2 diabetes later in life (41,42). Even though LGA is the most prevalent fetal growth disorder identified in diabetic pregnancy, it can also be linked to fetal growth restriction. Type 1 diabetes with a long history and poor control encompasses a wide range of clinical problems, the majority of which are connected to diabetic vasculopathy. Maternal vasculopathy has been associated with placental malfunction and impaired fetal growth (43,44).

Polycythemia, defined as a central venous hemoglobin concentration greater than 20 g/dl or a hematocrit value greater than 65%, is prevalent in newborns of diabetic mothers and is linked to glycemic management. Hyperglycemia is a potent stimulator of fetal erythropoietin synthesis, which is mediated by a reduction in fetal oxygen tension. Untreated newborn polycythemia can cause vascular sludging, ischemia, and infarction in key organs such as the kidneys and the nervous system (35).

15-25% of neonates born to women who had diabetes during pregnancy experience hypoglycemia during the first few weeks of life (45). When glycemic control is maintained during pregnancy (46) and childbirth, neonatal hypoglycemia is less common. Neonatal seizures, unconsciousness, and brain damage can all result from undiagnosed postnatal hypoglycemia (35).

Up to 50% of diabetic moms' newborns had low serum calcium levels (less than 7 mg/100 ml). These calcium alterations appear to be caused by functional hypoparathyroidism, although the specific etiology is still unknown. The rate of newborn hypocalcemia has been lowered to 5%, thanks to better glycemic control during pregnancy (35).

Hyperbilirubinemia affects about 25% of newborns of diabetic mothers, which is more than twice the prevalence in the general population. Several conditions contribute to hyperbilirubinemia in this category of newborns, but prematurity and poly-

cythemia are the most common. Increased red blood cell breakdown raises the risk of jaundice and kernicterus. Phototherapy is normally used to treat this condition; however, if bilirubin levels are highly elevated, exchange transfusions may be required (35).

Phospholipid assays show that more than 99% of healthy newborn infants have mature lung profiles by 37 weeks of gestation. In a diabetic pregnancy, however, the risk of respiratory distress may not decline until beyond 38.5 weeks of pregnancy. Until recently, the most common and serious morbidity in diabetic infants was neonatal respiratory distress syndrome. Improved prenatal maternal diabetes management and novel obstetrics procedures for timing and manner of delivery resulted in a substantial drop in its occurrence from 31% to 3% (47). The majority of studies suggest that offsprings of diabetic mothers experience significant biochemical and physiologic delays. Regardless of diabetes class, fetal lung maturity occurred later in pregnancies with poor maternal glycemic control, according to Tyden et al. (48) and Landon et al. (49).

**TABLE 3.** Perinatal morbidity in diabetic pregnancy

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| <ul style="list-style-type: none"> <li>• Hyperbilirubinemia</li> <li>• Hypoglycemia</li> <li>• Hypocalcemia</li> <li>• Respiratory distress</li> <li>• Cardiomyopathy</li> <li>• Polycythemia</li> <li>• Birth trauma</li> <li>• Excessive or insufficient birth weight</li> </ul> |
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## CONCLUSIONS

Increased susceptibility to GDM and exacerbation of preexisting maternal diabetes mellitus result from an inability to cope with the increased demand for insulin that physiologically occurs in pregnancy. This is due to an increase in the insulin antagonists levels such as prolactin, cortisol, leptin, and lactogen. Preexisting diabetes is linked to a variety of maternal and fetal problems and has an even worse fetal outcome than gestational diabetes. At delivery, fetal/neonatal complications can include macrosomia or growth restriction, respiratory distress syndrome, birth trauma, cardiomyopathy, or metabolic disorders. Thorough glycemic control during pregnancy and childbirth has been proven to reduce the appearance of these complications.

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