

Diabetic Pregnancy and Fetal Consequences

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Author Disclosure
Dr Teramo has disclosed that he answers patient questions on the NovoNordisk website. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Practice Gaps

1. There is a need for new strategies to help decrease risk of fetal and neonatal complications in diabetic pregnancy.
2. While important, it can be challenging to estimate fetal weight in diabetic pregnancy.

Abstract

Perinatal morbidity and mortality, congenital malformations, abnormal fetal growth, both spontaneous and iatrogenic preterm birth, hypoxic complications, and trauma during delivery are increased in diabetic pregnancies. Perinatal mortality in diabetic pregnancies is still three to five times higher than the perinatal mortality in the general population. Stillbirths during the last weeks of pregnancy are often considered unexplained, although recent studies indicate that most of these stillbirths are caused by fetal chronic hypoxia. Importantly, perinatal mortality has not changed during the past 3 decades in diabetic pregnancies, which emphasizes the need to find new methods and strategies to improve perinatal outcome. Congenital malformations have decreased in pregestational diabetic pregnancies because of general improvement of glycemic control among diabetic women. However, the rate of fetal malformations is still two to four times higher in type 1 and type 2 diabetic pregnancies than in the general population. Prepregnancy counseling decreases the risk of fetal malformations. Efforts should be made to improve the attendance of diabetic women in prepregnancy clinics. Fetal overgrowth during the last trimester of pregnancy is the most common fetal complication in diabetic pregnancies. Accurate estimation of fetal weight by ultrasound is especially difficult in macrosomic fetuses. Magnetic resonance imaging can be used to assess fetal total volume, shoulder width, and fat amount in addition to obtaining accurate pelvic measurements. More studies on the clinical use of magnetic resonance imaging in obstetrics are urgently needed. Increased fetal erythropoietin (EPO) level is an indicator of fetal chronic hypoxia, which can be detected antenatally by measuring amniotic fluid EPO concentration. Sufficiently large controlled studies are needed before amniotic fluid EPO measurement can be recommended for clinical use.

Objectives After completing this article, readers should be able to:

1. Describe the main fetal and neonatal complications in type 1 and type 2 diabetic pregnancies.
2. Explain the role of poor glycemic control in the pathogenesis of maternal and fetal complications in diabetic pregnancies.
3. Address the importance and problems in the estimation of fetal weight in diabetic pregnancies.
4. Discuss possible new strategies that could improve offspring outcomes in diabetic pregnancies.

Abbreviations

CI: confidence interval
EPO: erythropoietin
FHR: fetal heart rate
GDM: gestational diabetes mellitus
MRI: magnetic resonance imaging
OR: odds ratio

Introduction

Pregnancies complicated by maternal diabetes have major effects on the developing fetus throughout pregnancy. Congenital malformations, abnormal fetal growth, hypoxic

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complications, and trauma during delivery are increased in pregnancies of diabetic women. Although the exact pathogenetic mechanisms of fetal complications in diabetic pregnancies are not well understood in all instances, maternal hyperglycemia, and hence fetal hyperglycemia, is associated with several fetal complications (Table). In this review, early and late fetal complications, detection, management, and prevention in pregnancies complicated by maternal diabetes is discussed.

Perinatal Mortality

Perinatal mortality has remained unchanged at 2% to 4% in type 1 diabetic pregnancies during the past 30 years in most centers specializing in the care of diabetic pregnancies. (1)(2)(3) Congenital malformations (30%–40% of perinatal deaths), preterm birth (20%–30%), and intrauterine hypoxia (20%–30%) are the main causes of

perinatal deaths in type 1 diabetic pregnancies. Detection of lethal fetal malformations by sonography decreases the perinatal mortality by ~0.5 percentage units when these pregnancies are interrupted before 20 weeks' pregnancy (unpublished observation).

The stillbirth rate in type 1 diabetic pregnancies increased linearly during the last weeks of pregnancy before fetal electronic monitoring was available, reaching 20% at term. (4) The pathogenesis of this increasing trend of stillbirths toward the end of pregnancy is unknown. Although the stillbirth rate has been considerably lower during recent decades than in the 1950s, unexplained stillbirths still occur during the last weeks of pregnancy in pregestational diabetes pregnancies. (3) Maternal diabetes remains an independent risk factor of fetal death. (5) Most of the stillbirth fetuses before 32 weeks' gestation are growth restricted. (3) However, in a recent birth registry study from Norway, the stillbirth rate before 37 weeks' gestation in type 1 diabetic pregnancies did not differ from the stillbirth rate of the background population. (6) In contrast, the stillbirth rate in term pregnancies was five times higher in type 1 diabetic pregnancies than in the general population. Also infant deaths during the first year after birth was higher in type 1 diabetes pregnancies than in the general population. (6) Moreover, both the stillbirth rate and perinatal mortality in type 1 diabetic pregnancies did not decrease significantly between 1985 and 2004 in Norway.

Table. Fetal and Neonatal Consequences of Fetal Hyperglycemia and Hyperinsulinemia in Diabetic Pregnancies

Increased fetal substrate uptake
Increased risk of fetal macrosomia
Increased risk of fetal shoulder dystocia at delivery
Increased risk of fetal trauma at delivery (Erb palsy, fractures)
Increased risk of stillbirth at delivery
Increased risk of neonatal asphyxia at delivery
Increased risk of maternal trauma
Increased rate of cesarean deliveries
Decreased rate of intrauterine growth restriction
Fetal Chronic Hypoxia
Increased oxygen consumption and decreased arterial oxygen content
Increased fetal erythropoietin synthesis
Fetal polycythemia
Increased nucleated red cell count in cord blood
Decreased or depleted fetal iron stores
Increased fetal and neonatal distress and asphyxia
Increased risk of stillbirth
Delayed lung maturation
Increased risk of neonatal respiratory distress syndrome
Increased risk of neonatal transient tachypnea
Neonatal hypoglycemia
Increased risk of hypoglycemia during the first days after birth

Fetal Malformations

There is now general agreement that poor maternal glycemic control (hyperglycemia) at conception and during the first trimester of pregnancy is the main cause of fetal major malformations in diabetic pregnancies. (7)(8)(9)(10) Poor glycemic control increases also the miscarriage risk in these pregnancies. (7) Hyperglycemia in the developing fetus alters lipid metabolism, generates an excess of reactive oxygen species, and activates apoptosis, which all can result in fetal malformations. (11) Although the risk of fetal malformations has decreased during the past 3 decades due to improved glycemic control in women with diabetes, (8) the rate of malformations is still two to four times higher in type 1 and type 2 diabetic pregnancies than in the general population. (8)(9)(10)(12)

The most common malformations in diabetic pregnancies occur in the heart, central nervous system, and urinary system. (13) Multiple malformations are also common in fetuses of pregestational diabetic women. Caudal regression syndrome, although rare, is seen in diabetic pregnancies only. There is not an increased risk of

malformations in the offspring of women with gestational diabetes (GDM), although there are reports that the risk of congenital malformations is slightly increased in women diagnosed with GDM. However, malformations in these pregnancies are likely to occur in hyperglycemic women with undiagnosed type 2 diabetes.

Preconception care is important in type 1 and type 2 diabetic pregnancies because fetal malformations are formed early during fetal development, (14) usually before first antenatal visit. A threefold reduction in the risk of major malformations has been reported in offspring of women who received prepregnancy care compared with offspring of women without such care. (15) Unfortunately, approximately half of pregnancies are not planned, and therefore only 30% to 40% of the diabetic patients attend a clinic for prepregnancy care. Folic acid and vitamin supplementation is recommended to all women in reproductive age. (16) This is especially important in type 1 and type 2 diabetes patients. At the prepregnancy visit, diabetes complications should be evaluated, and the risk of pregnancy and fetal complications should be discussed in addition to controlling the glycemic status. (17) Most centers recommend that the HbA_{1c} should be less than 7% before conception, but this cannot be achieved in all type 1 diabetes patients. The rate of major malformations in offspring of type 2 diabetic pregnancies does not differ from the rates in offspring of type 1 diabetic pregnancies. (18)

A thorough sonographic examination of the fetal structures should be offered to all diabetic patients at 18 to 20 weeks' gestation. If the glycemic control is not optimal in early pregnancy (HbA_{1c} >8%), a fetal echocardiography is recommended at ~20 weeks' gestation. Even in patients with poor glycemic control in early pregnancy (HbA_{1c} >10%), 85% to 90% of the fetuses do not have major malformations. (8)(9) Therefore, a high HbA_{1c} value alone in early pregnancy should not be an indication to interrupt the pregnancy.

Preterm Birth

Poor glycemic control (hyperglycemia) has been reported to increase the risk of spontaneous preterm birth rate in type 1 diabetic pregnancies. (19) Pre-eclampsia and diabetic nephropathy can cause fetal growth restriction in diabetic pregnancies, which increases iatrogenic preterm birth because severe early pre-eclampsia necessitates delivery on maternal or fetal indications before 30 weeks' gestation. Glucocorticoids also should be used in threatened preterm labor in diabetic pregnancies. However, glucocorticoid administration to women with pregestational or insulin-treated gestational diabetes can result in long-lasting hyperglycemia and increased risk of ketoacidosis.

Increasing the insulin dose by 30% to 50% for a few days is often necessary when glucocorticoids are used in diabetic pregnancies. (17)

Fetal Growth

Fetal overgrowth during the last trimester of pregnancy is the most common fetal complication in pregnancies of women with diabetes. The birthweight should be expressed as relative to the gestational age. Large for gestational age is best defined as more than 2 SD (>97.7th percentile) above the mean birthweight of a standard population, but birthweight more than 90th percentile is also frequently used. Small for gestational age is defined as more than 2 SD (<2.3th percentile) below the reference mean. (20) Ethnicity, genetic, and environmental factors (eg, maternal BMI, parity, smoking, and nutrition) influence the size of the fetus.

Fetal macrosomia is often defined as birthweight more than 4,000 g, but the foregoing definition of large for gestational age is preferred as the definition for macrosomia. At present, 18% of newborn infants weigh more than 4,000 g at birth in Finland. The corresponding figure in the United States is 9%. In type 1 diabetic pregnancies, the rate of macrosomia defined as more than 2 SD above the mean of the reference population is more than 30% in Finland and Sweden. (2)(21) The birthweight distribution in type 1 diabetic pregnancies is normal Gaussian but shifted to the right (22)(23), that is, the number of small for gestational age fetuses in diabetic pregnancies is lower than in the general population. In Sweden, 3% of birthweights were below the 10th percentile in type 1 diabetic pregnancies compared with 9.1% in the general population. (23)

Fetal hyperinsulinemia is the main cause of fetal overgrowth in diabetic pregnancies. (24)(25) Chronic hyperinsulinemia in euglycemic rhesus monkeys results in fetal macrosomia and organomegaly. (24) Interestingly, macrosomic fetuses of nondiabetic mothers with a birthweight more than 2 SD above the mean of the background population are not hyperinsulinemic. (25) Fetal body composition of diabetic mothers differs often from fetal body composition of healthy mothers. (26) Macrosomic fetuses of diabetic mothers have increased adipose tissue and organomegaly, but their head size is not increased. Severe shoulder dystocia can result in brachial plexus injury during vaginal delivery, which occurs 10 times more often in offspring of type 1 diabetic pregnancies than in the general population. (2)(27) The majority of brachial plexus injuries and fractures occurs in fetuses weighing more than 4,000 g at birth. (28)

The most accurate method for pregnancy dating is by measuring the fetal crown to rump length at ~10 to 12 weeks' gestation. Accurate dating is important when estimating the fetal weight in diabetic pregnancy during the last trimester of pregnancy. However, estimating the fetal weight by sonography has been disappointing. (29) The mean error in the estimation of fetal weight by sonography is 10% to 15% for normal weight fetuses, but it increases to 15% to 20% when predicting birthweights more than 4,000 g. (30) For example, a fetus with an estimated weight of 4,000 g by ultrasound can actually weigh 5,000 g, which can have serious consequences for both the mother and the child. Sonographic models using three or four fetal biometric measurements are more accurate than methods using abdominal circumference alone or two biometric measurements. (30)

Fetal weight, shoulder width, and pelvic capacity can be measured using magnetic resonance imaging (MRI), (31)(32)(33) but large clinical studies about the usefulness of MRI in obstetrics are still lacking. It is now also possible to measure fetal fat volume and body composition using MRI. (34) Studies for evaluating the clinical value of MRI in detecting fetal macrosomia and abnormal body composition are urgently needed, particularly in diabetic pregnancies.

Fetal growth restriction in diabetic pregnancies occurs mainly in women with nephropathy, in whom preeclampsia often further complicates the outcome of their offspring. Because diabetes also increases the birthweight of growth-restricted fetuses, it is possible that growth restriction of fetuses of type 1 diabetic women should be defined differently from pregnancies of nondiabetic pregnancies. Amniotic fluid erythropoietin (EPO) is a specific indicator of fetal chronic hypoxia. (35) We have shown that relative birthweight correlates in a U-shaped fashion with amniotic fluid EPO concentration in type 1 diabetic pregnancies. (36) Amniotic fluid EPO concentration correlated negatively with birthweight when the birthweight z score was below -0.6 SD units ($r = -0.63$, $P < .001$) but positively when the birthweight z score was above $+1.0$ SD units ($r = 0.32$, $P = .001$). (36) This could explain why unexpected stillbirths occur also in fetuses with "normal" birthweight (birthweight z score above -2 SD but below $+2.0$ SD). More studies are clearly needed to evaluate the optimal birthweight in diabetic pregnancies.

Fetal Chronic Hypoxia

Clinical signs of fetal hypoxia (abnormal fetal heart rate [FHR] changes, umbilical artery acidosis, and low Apgar scores at birth) are more common in diabetic than nondiabetic pregnancies. (37) Neonatal polycythemia and

increased nucleated red cells in cord blood occur also frequently in pregestational diabetic pregnancies. (37) The fetus adapts to chronic hypoxia by redistributing its cardiac output and maintaining its blood flow to the brain and heart and by increasing its EPO synthesis to increase the oxygen-carrying capacity in the blood. Both elevated fetal plasma and amniotic fluid EPO levels are markers of intrauterine chronic hypoxia. (35) Fetal EPO levels are frequently elevated in type 1 diabetic pregnancies, (36) which provides evidence that fetal chronic hypoxia often complicates these pregnancies.

Increased erythropoiesis requires increased amounts of iron. Iron is therefore preferentially absorbed from fetal iron stores during increased production of red cells. (38) The iron stores of stillbirth fetuses of diabetic mothers are extremely low or totally depleted, (39) suggesting that chronic hypoxia is the main cause of late fetal deaths. In line with this are the observations that the iron distribution is abnormal and the ferritin levels are low in newborn infants of diabetic mothers. (39) Fetal chronic hypoxia and associated fetal iron deficiency may be responsible for abnormal neurodevelopment in offspring of diabetic mothers. (40)

In the fetal sheep, both hyperinsulinemia and hyperglycemia result in an increase in fetal oxygen consumption and a fall in arterial oxygen content. (41)(42) Fetal insulin levels correlate directly with fetal EPO levels in diabetic pregnancies, (43) suggesting that hyperinsulinemia also results in fetal chronic hypoxia in human pregnancies. Maternal HbA_{1c} levels obtained during the last month before delivery in type 1 diabetic pregnancies correlates directly with fetal EPO levels, (35)(43) emphasizing the importance of maintaining good glycemic control throughout pregnancy. Forced stepwise multiple regression analysis has shown that both maternal hyperglycemia (ie, fetal hyperglycemia) and fetal hyperinsulinemia independently can cause fetal chronic hypoxia as indicated by elevated fetal EPO levels. (43)

The fact that perinatal mortality has not decreased in diabetic pregnancies in most centers during the past few decades indicates that the current methods and strategies for fetal surveillance are not satisfactory. Twice weekly nonstressed testing of FHR has been suggested for prevention of stillbirths during the last weeks of pregnancy. (44) However, several studies have shown that nonstressed FHR and biophysical testing have limited value in diabetic pregnancies, (45)(46) which is probably explained by different pathogenetic mechanism of fetal hypoxia in diabetic pregnancies compared with fetal hypoxia resulting from placental insufficiency. For the same reason, studies on uterine or umbilical artery Doppler flow assessment have concluded that this method is not

reliable in fetal surveillance in diabetic pregnancies with the possible exception of pregnancies complicated by pre-eclampsia or growth restriction. (47)

Exponentially increasing EPO levels in the amniotic fluid is associated with fetal hypoxia (for review, see Teramo and Widness). (35) In our own study, abnormal high amniotic fluid EPO levels were detected antenatally in 21 of 156 (13.5%) consecutive type 1 diabetic pregnancies. (36) High amniotic fluid EPO levels predicted fetal macrosomia (odds ratio [OR] 5.4, 95% confidence interval [CI] 1.9–15.3), obstructive cardiomyopathy (OR 12.5, 95% CI 2.6–59.3), neonatal hypoglycemia (OR 11.3, 95% CI 3.8–33.7) and NICU admission (OR 3.4%, 95% CI 1.1–10.8). (36) Fetal EPO synthesis increases regardless of the etiology of hypoxia. It is therefore possible to detect fetal chronic hypoxia antenatally by amniotic fluid EPO measurement in type 1 diabetic pregnancies. (35) However, sufficiently large controlled studies should be performed before possible clinical benefits of amniotic fluid EPO measurements in diabetic pregnancies can be recommended.

Timing and Mode of Delivery

The American College of Obstetricians and Gynecologists recommends elective cesarean delivery when the estimated fetal weight is more than 5,000 g in pregnancies of nondiabetic women and when the estimated weight is more than 4,500 g in diabetic women. (48) Arrest of descent of the fetal head or prolonged second stage of labor are also indications for cesarean delivery when the estimated fetal weight is more than 4,500 g. Vacuum extraction and forceps delivery increase the risk of shoulder dystocia of macrosomic fetuses in diabetic pregnancies.

The proportionally high stillbirth rate in term type 1 diabetic pregnancies has influenced clinical guidelines for timing of delivery. The National Institute for Health Care and Excellence guidelines in the United Kingdom recommends that women with pregestational diabetes should be offered induction of labor or elective cesarean delivery at completed 38 weeks' pregnancy. (49) The American Diabetes Association recommends that diabetic women with good glycemic control and without other complications can wait for spontaneous labor until 39 to 40 weeks' pregnancy. (50) National guidelines in Norway recommend induction of labor at approximately 40 weeks in women with pregestational diabetes when indications for earlier induction are not present. (6) Because unexpected stillbirths still occur and perinatal mortality has not decreased during the past 30 years, new strategies for identifying diabetic pregnancies with a high risk of fetal hypoxic complications needs to be developed.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the effects on the fetus and/or newborn infant of maternal diabetes 2 mellitus (including gestational diabetes) and their management
- Know the hormonal factors that affect intrauterine fetal growth



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1. A mother who has history of diabetes controlled by insulin is pregnant and asks about the risk of fetal malformations. Which of the following statements regarding risk of fetal malformation in diabetic pregnancy is correct?
 - A. The highest risk of a major malformation occurs when there is poor maternal glycemic control during the second and third trimesters.
 - B. The rate of malformation is two to four times higher in type 1 and type 2 pregnancies than in the general population.
 - C. The most common malformations in diabetic pregnancies involve the upper and lower extremities.
 - D. The risk of malformations in gestational diabetes is equal to the risk found in type 1 and type 2 diabetes.
 - E. Unlike typical pregnancies, folic acid should be avoided in pregnant women with type 1 diabetes, as the risk of folic acid excess is higher than that of neural tube defects.
2. A 28-year-old woman is pregnant with her second child. Her first pregnancy resulted in a spontaneous preterm delivery at 28 weeks' gestational age. Her second pregnancy is complicated by diabetes. Which of the following is true regarding her risk of preterm birth?
 - A. One risk of preeclampsia and diabetic nephropathy is fetal growth restriction, which may increase the risk of iatrogenic preterm birth, if there are fetal indications.
 - B. As her first child was born preterm, it is highly unlikely that she will have a second preterm child, as one mother having two preterm births in a row is a rare occurrence.
 - C. Spontaneous preterm birth is most likely to be an increased occurrence in gestational diabetes, as compared to type 1 diabetic pregnancies.
 - D. If preterm birth is likely to occur, it is important to remember that glucocorticoids are contraindicated in diabetic mothers.
 - E. While preterm birth is an increased risk in diabetic pregnancies, late preterm birth is generally more acceptable than non-diabetic pregnancies, as these infants tend to be larger and more mature for their gestational age.
3. A pregnant woman with diabetes is evaluated at 35 weeks' gestational age. Fetal growth parameters are estimated using physical examination and ultrasound. Which of the following statements regarding growth in diabetic pregnancies is correct?
 - A. Ultrasound estimate of fetal weight is more accurate in diabetic pregnancies than in non-diabetics due, particularly in larger fetuses more than 4,000 grams, as there is a higher ratio of solid mass to fluid.
 - B. Fetal hyperinsulinemia is the main cause of fetal overgrowth in diabetic pregnancies.
 - C. The most accurate method for pregnancy dating is fetal crown-rump length at 18 to 20 weeks' gestational age.
 - D. Although macrosomia is more common in type 1 diabetic pregnancies at 18% to 30%, the incidence of small for gestational age is also increased to 10% to 25%.
 - E. In macrosomic infants of diabetic mothers, the head size is disproportionately increased up to 30% of normal size, compounding risk of delivery problems.
4. A 39-week-gestational-age male infant is born by spontaneous vaginal delivery to a mother who had gestational diabetes which was diet controlled. He develops respiratory distress and an evaluation includes hematocrit which is noted to be 72% two hours after birth. Which of the following statements regarding this clinical circumstance is correct?
 - A. A hematocrit at age 2 hours is more reflective of the mother's hematocrit and should not be considered as part of the diagnostic work-up of an infant.

- B. While polycythemia can occur in type 1 diabetic pregnancies, it is not associated with gestational diabetes and is likely to arise from a different etiology in this scenario.
- C. This infant may have had some degree of chronic hypoxia and increased erythropoietin synthesis in order to increase oxygen carrying capacity.
- D. This infant's ferritin levels are likely to be abnormally elevated.
- E. Erythropoietin would have been rapidly consumed by this fetus and if an amniotic fluid sample was obtained before delivery, it is likely that erythropoietin levels in the fluid would be low or non-existent.
5. A mother presents with intermittent contractions to the clinic at 40 weeks' gestational age. She has gestational diabetes which has been poorly controlled, and is suspected to have risk of a macrosomic fetus based on recent visits. Which of the following regarding her delivery course and management is correct?
- A. Although her infant may be macrosomic, the risks of non-spontaneous labor induction on respiratory outcomes balance out risks of macrosomia, and therefore, delivery should be deferred until spontaneous labor or induction at 41 weeks.
- B. Fetal weight estimates should not have a role in decisions about mode of delivery due to their inaccuracy.
- C. While cesarean delivery is more common in diabetic pregnancies, they can be avoided in situations when the infant is mildly macrosomic (>4,500–5,000 grams) with vacuum extraction or forceps assistance, with decreased risk of shoulder dystocia.
- D. Cesarean delivery is probably indicated when the estimated fetal weight is more than 4,500 grams and there is arrest of descent of the head or a prolonged second stage of labor.
- E. A key principle in the management of diabetic mothers is to disregard estimated fetal weight in the decision to perform cesarean section due to its inaccuracy and lack of ability to predict clinical complications.

Parent Resources from the AAP at HealthyChildren.org

- English: <http://www.healthychildren.org/English/ages-stages/prenatal/Pages/Tests-During-Pregnancy.aspx>
- Spanish: <http://www.healthychildren.org/spanish/ages-stages/prenatal/paginas/tests-during-pregnancy.aspx>

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