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DIABETES AND PREGNANCY (CJ HOMKO, SECTION EDITOR)

Stillbirth in the Pregnancy Complicated by Diabetes

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Abstract Pregestational diabetes currently complicates 4 % of pregnancies, while gestational diabetes complicates approximately 8 % of pregnancies. Increased risk of stillbirth in diabetic pregnancies has been a well-known and recognized complication for decades. While stillbirth rates for diabetic pregnancies have decreased due to screening, treatment, and antenatal surveillance of these patients, about 4 % of all stillbirths remain attributable to diabetes, and diabetic pregnancies continue to be at increased risk for perinatal mortality. The purpose of this article is to review the literature on the epidemiology, pathophysiology, and prevention, as well as future research, of diabetes-associated perinatal mortality.

Keywords Stillbirth · Pregestational diabetes mellitus · Gestational diabetes mellitus · Hemoglobin A1c · Hyperglycemia · Hypoglycemia

Introduction

Management of diabetes during pregnancy has improved significantly since the beginning of the twentieth century, when successful pregnancy in women with pregestational diabetes was rare. In fact, perinatal mortality was as high as 65 % and maternal mortality was approximately 35 % [1]. After the discovery of insulin, maternal mortality decreased significantly; however, perinatal mortality did not decrease until the 1960s. The improvement in perinatal mortality rates can be attributed to modern prenatal care, including more stringent monitoring of serum glucose, implementation of antepartum testing and ultrasound, safer cesarean delivery, and the timely delivery of fetuses that show evidence of early intrauterine compromise. Unfortunately, other factors that independently contribute to the risks of stillbirth are presently on the rise in diabetic pregnancies, including obesity (increases risk from 2 to 4.6-fold) [2–4], previous cesarean delivery (doubles the risk) [5, 6], advanced maternal age [7–9], congenital and fetal abnormalities [10•, 11–13], and fetal growth restriction [14•, 15, 16]. With the burgeoning epidemic of obesity and the changing screening guidelines to diagnose diabetes in pregnancy [17–19], the number of pregnancies complicated by gestational and pregestational diabetes is expected to increase significantly in the future. Thus, understanding the pathophysiology, as well as developing individualized approaches in the prevention of stillbirths in pregnant women with diabetes, is crucial.

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Epidemiology

Stillbirth is defined as fetal death at or greater than 20 weeks of gestation or birth weight of 350 g or greater. On the other hand, perinatal mortality is defined as the number of stillbirths plus the number of neonatal deaths up to 28 days of life [20]. Diabetes during pregnancy can be divided into gestational and pregestational. Gestational diabetes (GDM) is diabetes diagnosed during pregnancy, while pregestational diabetes comprises type 1 and type 2 diabetes mellitus (DM).

Type 1 Diabetes

Recent studies have shown that patients with type 1 diabetes overall have a fivefold increased risk of stillbirth compared to women who do not have diabetes. The relative risks of

stillbirth and perinatal mortality in patients with type 1 diabetes vary and are summarized in Table 1. The majority of the data come from national registries and from retrospective studies [21–27].

Type 2 Diabetes

Type 2 DM also is a significant risk factor for stillbirth. The risk of stillbirth and perinatal mortality in women with type 2 diabetes are also summarized in Table 2. Some reports do not distinguish between type 1 and type 2 DM and combine patients with pregestational diabetes when comparing rates of stillbirth and perinatal mortality. Table 3 summarizes the relative risk of stillbirth and perinatal mortality for women with any form of pregestational diabetes.

Perinatal mortality in patients with type 2 DM appears to be at least as high as in patients with type 1 DM, and some reports suggest that it may be even higher. Both Cundy et al. [28] and Clausen et al. [29] compared perinatal mortality between women with type 1 DM and type 2 DM, and both reports state that the relative risk for perinatal mortality is 3.8–3.9 for type 2 DM compared to type 1 DM. However, other studies [32, 34] have failed to confirm these findings. A large meta-analysis of 33 studies failed to demonstrate a difference in stillbirth, perinatal, and neonatal mortality rates in type 2 DM compared to type 1 DM [35].

The risk of congenital abnormalities also appears to be much higher in pregestational diabetes than the general population. Some studies excluded congenital abnormalities when reporting rates of stillbirth, while others have not. Whether congenital abnormalities are present or not, the risk of stillbirth and overall perinatal mortality among mothers with pregestational diabetes is higher than that of the general population [28, 29].

Gestational Diabetes

Whether GDM is a risk factor for stillbirth is debatable. Some studies indicate that GDM may be a risk factor for stillbirth and perinatal mortality, although this risk does not appear to be as increased as with pregestational diabetes. Earlier studies [36, 37] demonstrated a fourfold increased risk of perinatal mortality. A more recent case–control study by Aberg et al. [38] reported that previous pregnancies of women diagnosed with GDM had higher rates of stillbirth than nondiabetic women (14.9 per 1000 vs. 6.5 per 1000, OR 1.56, 95 % CI 1.12–2.19). This finding indicates that one explanation may be that these women likely had undiagnosed GDM during previous pregnancies.

Similarly, Wood et al. [39] demonstrated that women diagnosed with type 2 DM after pregnancy had higher rates of stillbirth than nondiabetic controls. However, more recent studies [40, 41] point out that diagnosing and treating GDM during pregnancy likely reduces perinatal mortality rates. Interestingly, Langer et al. [42] compared women who were diagnosed with GDM after 37 weeks (and hence untreated) with women who were treated for GDM and women without diabetes. The stillbirth rates (per 1000 births) in untreated, treated, and nondiabetic groups were 5.4, 3.6, and 1.8, respectively. While there definitely was a trend for women with untreated diabetes being at higher risk for stillbirth than treated women and women from the general population, these rates failed to reach statistical significance, likely due to small sample size. Similarly, in the large Maternal Fetal Medicine Unit trial, Landon et al. [43] did not find a difference in rates of stillbirth between treated and untreated women (there were no stillbirths or neonatal deaths in either group).

A large study analyzing U.S. National Center for Health Statistics data from 10,733,983 births between 1995 and 1997 reported that the risk of stillbirth in pregnancies complicated by diabetes (both gestational and pregestational) is higher than in the nondiabetic population 5.9 vs. 4.0 per 1000 births, respectively [44]. This study did not distinguish between gestational and pregestational diabetes; however, regardless of diabetes type, the stillbirth rate in women with pregnancies complicated by diabetes was higher than that in the nondiabetic population.

Table 1 The risk of stillbirth in women with type 1 diabetes

Study	Number of patients	Study design	Years of study	Country	Stillbirth (RR)	Perinatal mortality (RR)
Lauenborg et al. [21]	1361	Retrospective cohort	1990–2000	Denmark	–	
Eidem et al. [22]	1307	Retrospective cohort	1985–2004	Norway	3.6	2.9
Persson et al. [23]	5089	Prospective cohort	1991–2003	Sweden	3.3	3.3
Jensen et al.[24]	1215	Prospective cohort	1993–1999	Denmark	4.7	4.1
Dos Santos Silva et al. [25]	1125	Retrospective cohort	1979–1995	Scotland	4.7	2.4
Panney et al. [26]	213	Prospective cohort	1998–1999	Scotland	3.6	3.7
Casson et al. [27]	462	Retrospective cohort	1990–1994	UK	5.0	4.3

Table 2 The risk of stillbirth in women with type 2 diabetes

Study	Number of patients	Study design	Years of study	Country	Stillbirth (RR)	Perinatal mortality (RR)
Cundy et al. [28]	434	Observational study	1985–1997	New Zealand	2.5	3.8
Clausen et al. [29]	61	Retrospective cohort	1996–2001	Sweden	9.0	–
De Valk HW et al. [30]	66	Retrospective cohort	1992–2006	Netherlands	–	4.5
Dunne et al. [31]	183	Retrospective cohort	1990–2002	UK	2.3	2.5

Pathophysiology

The pathophysiology of stillbirth in diabetic pregnancies is complex and appears to be multifactorial. Many different causes have different pathways that all lead to either stillbirth or neonatal death. Figure 1 depicts the most commonly studied pathways. While many of the pathways cross each other, some directly result in stillbirth.

Maternal Vascular Disease and Other Coexisting Maternal Conditions

Both type 1 and type 2 diabetes often coexist with other medical conditions. Type 1 DM usually starts early in life and is due to an autoimmune destruction of pancreatic beta cells. Because it is an autoimmune disease, many patients with type 1 diabetes develop other autoimmune diseases, most commonly autoimmune thyroiditis and celiac disease. Type 2 DM usually presents itself later in life and is characterized by insulin resistance or impaired insulin secretion leading to hyperglycemia. Type 2 DM is usually associated with obesity, hypertension, and hypercholesterolemia (metabolic syndrome). Also, poorly controlled DM (both types 1 and 2) can result in long-standing hyperglycemia, which is associated with the development of microvascular complications. Retinopathy, neuropathy, and nephropathy are the most common end-organ damage complications.

In patients with microvascular complications, placental insult will likely occur early in pregnancy during trophoblastic invasion of spiral arterioles. A high glucose concentration will also lead to excess reactive oxygen species (ROS). The presence of ROS can result in cell death and tissue damage and thus influence placental development [45]. Furthermore, failed trophoblast invasion results in early pregnancy loss. Blood flows from the uterine arteries into the maternal spiral arteries and then into the low-resistance placental vessels. Shallow trophoblast invasion results in reduced uteroplacental blood flow and increased resistance which can be identified by Doppler interrogation of the uterine vessels. Superficial trophoblast invasion results in decreased maternal spiral artery vascular remodeling [46], which later results in poor villous differentiation and maturation. This results in a smaller-than-expected placenta and fetus (fetal growth restriction), as well as preeclampsia and abruption. Any of these complications (or combinations of these complications) can contribute to the pathophysiology resulting in stillbirth. Interestingly, many studies have shown that congenital malformations in diabetic mothers result from oxidative stress [47•] due to the generation of ROS. Major congenital malformations are increased in patients with pregestational diabetes and are a major reason for stillbirth [48••, 49, 50].

Hyperglycemia

Regardless of the type of maternal diabetes, maternal hyperglycemia leads to fetal hyperglycemia, which in turn leads to fetal hyperinsulinemia. High cord blood insulin levels are often observed in women whose DM is not adequately treated during pregnancy. High levels of fetal insulin and high glucose, amino acid, and lipid concentrations result in adipocyte mitogenesis and increase underlying fetal fat accumulation. This results in disproportionate fetal growth, which increases fetal oxygen demand. An imbalance between fetal oxygen demand and fetal oxygen supply results in fetal and placental hypoxia and fetal metabolic acidosis [51, 52].

Datta et al. [53] reported that the infusion of glucose into normal and diabetic pregnant women during labor can result in neonatal hypoxia and acidosis. In addition to fetal acidosis, fetal hypoxia can stimulate the secretion of vascular endothelial growth factors (VEGFs) and fibroblast growth factors

Table 3 The risk of stillbirth in women with any pregestational diabetes

Study	Number of patients	Study design	Years of study	Country	Stillbirth (RR)	Perinatal mortality (RR)
Macintosh et al. [32]	2359	Prospective cohort	2003–2003	UK	4.7	3.8
Hawthorne et al. [33]	113	Prospective cohort	1994	UK	–	5.4
Boulot et al. [34]	435	Prospective cohort	2000–2001	France	–	6.3

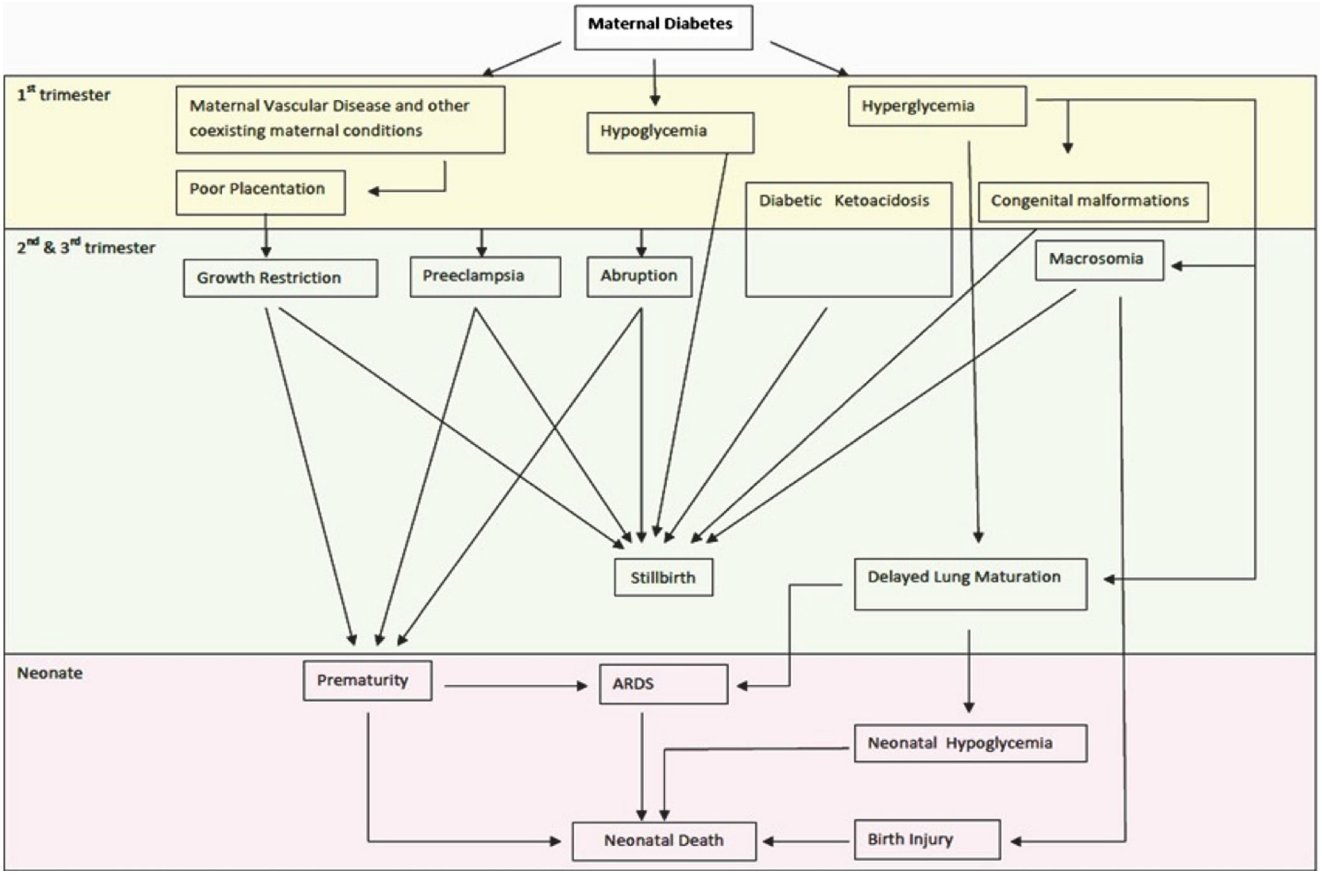

Fig. 1 Common pathways that lead to stillbirth and neonatal death

(FGFs). When diffused across the placenta, these factors cause the hypervascularization of placental vessels in an attempt to increase the maternal–fetal exchange surface. The hypervascularization of placental villi is a common placental pathological change that indicates prolonged intrauterine fetal hypoxia. Fetal hypoxia regulates the production of nitrous oxide (a potent vasodilator), which results in the further dilation of villous vessels. Sometimes, these villous vessels do not mature (villous immaturity for given gestational ages is a common histological finding in diabetic placentas) and the placenta therefore does not support the rapidly growing fetus. Fetal adaptation to chronic hypoxia results in extramedullary hematopoiesis and elevated cord blood erythropoietin levels. Persistent fetal hypoxia and acidemia may result in stillbirth.

Hypoglycemia

Hypoglycemia can also be dangerous during pregnancy. Hypoglycemia is defined as blood sugar level <45 mg/dL [54]. Almost 75 % of those patients who undergo treatment for diabetes during pregnancy experience at least one episode of hypoglycemia [55]. While it is unclear if hypoglycemia can directly cause fetal death, it is known that glucose is a main substrate for fetal growth and development; therefore, it is reasonable to speculate that persistent maternal hypoglycemia likely results in decreased uteroplacental blood flow and fetal growth restriction [56].

Other

Practitioners often find no clear etiology for stillbirth. However, fetal autopsy can sometimes provide clues and explanations for fetal death. Many fetuses of diabetic mothers develop in utero cardiomegaly and a thickened interventricular septum [57]. Postmortem reports of stillborn infants from women with diabetes showed the infants to have heavier hearts and thicker ventricular walls [58]. An increased level of circulating fetal insulin results in glycogen deposition in the myocardium. Echocardiographic studies in these infants suggest that a large number of these infants have evidence of cardiomyopathy [59]. Many experts hypothesize that cardiomyopathy can be a possible reason for unexplained stillbirth in diabetic mothers. Other common cardiovascular malformations attributed to maternal hyperglycemia include ventricular septal defects and conotruncal abnormalities of the heart [60–62]. Cardiovascular malformations account approximately two third of all malformations found in infants of diabetic mothers.

Malformations of other organ system such as central nervous system (neural tube defects), musculoskeletal system malformations such as caudal regression syndrome, and gastrointestinal malformations like small left colon and imperforate anus are also more common in women with pregestational diabetes. Since approximately 50 % of perinatal deaths in diabetic pregnancies are attributed to congenital malformations, autopsy should be offered for all unexplained fetal deaths. In a recent study by the Stillbirth Collaboration Research Network, abnormal findings during autopsy can be identified in 31.4 % of stillbirths [48••]. Therefore, offering perinatal postmortem examination to families in important part of work up of etiology of stillbirth.

Neonatal Mortality

The major cause of neonatal death in diabetic pregnancies is prematurity. Fetal hyperglycemia and hyperinsulinemia interfere with surfactant biosynthesis by type 2 pneumocytes and the maturation of fetal lungs [63, 64]. Newborns from diabetic mothers are at increased risk of respiratory distress syndrome and neonatal death. Metabolic alterations found in infants of diabetic mothers, including hypoglycemia, hypocalcemia, hypomagnesemia, and hyperbilirubinemia, can contribute to infant mortality if not treated appropriately. Other reasons for neonatal mortality include birth injury and birth asphyxia, as well as congenital malformations and thrombosis of fetal vessels (which likely results from fetal polycythemia and hyperviscosity).

Prevention of Stillbirth

One of the goals of St. Vincent's Declaration [65] was to "Achieve pregnancy outcomes in women with diabetes that approximate those of women without diabetes." Unfortunately, more than 20 years have passed, yet this goal has not yet been met. Significant progress has been made since that time, and there is some evidence that pregnancies managed in specialized centers tend to have better outcomes. However, rates of congenital abnormalities and perinatal mortality are still higher than those of the general population [29, 31, 66]. The prevention strategy should focus on the specific pathways that lead to stillbirth; however, achieving early, preferably prior to conception, strict glycemic control is the single most important goal for women with diabetes attempting pregnancy.

Maternal Vascular Disease or Other Maternal Coexisting Conditions

As described earlier, women with preexisting microvascular complications are at increased risk for a shallow trophoblast invasion that subsequently results in preeclampsia, fetal growth restriction, and placental abruption. These three common conditions have been recently grouped into a specific syndrome termed ischemic placental disease (IPD) [67, 68]. Recently, extensive research has targeted the pathways that lead to IPD. Since hyperglycemia-induced oxidative stress plays a major role in inadequate placental attachment, one would assume that the administration of antioxidants (such as vitamins C and E) at the time of implantation would help prevent poor placentation. Unfortunately, antioxidant supplementation trials have failed to show risk reduction in IPD [66–72]. The results from aspirin (FDA category C) trials are mixed; however, it appears to be effective in a subgroup of patients with evidence of IPD during previous pregnancies [73, 74]. Many women with microvascular complications have chronic hypertension, which should be appropriately treated with antihypertensive medications that are considered acceptable for pregnancy. Women with evidence of intravascular complications should be screened for fetal growth restriction with serial ultrasounds during pregnancy. If fetal growth restriction is identified, then Doppler interrogation of the umbilical artery should be performed to evaluate the function of the fetoplacental unit. Early umbilical artery Doppler abnormalities may identify fetuses at risk for stillbirth and aid in determining the timing of delivery.

Hyperglycemia

Preconception Goals

High hemoglobin A1c (HbA1c) during early pregnancy has been associated with an increase in congenital abnormalities. Pregnancies complicated by diabetes confer an increased risk of miscarriage and congenital malformations, the prevalence of the latter noted to be as high as 20 % when hemoglobin A1C values are 8.5 % or greater [75–77]. Preconception counseling and treatment are recommended for all women with pregestational diabetes to achieve HbA1c values between 6.0 and 7.0 %. This level is recommended to decrease the risk of congenital malformations and miscarriage; however, obtaining an early HbA1c value has not been useful when predicting adverse pregnancy outcomes. Nielsen [78] studied 474 pregestational diabetic pregnancies with early HbA1c values and found that the area under the curve of a receiver operating characteristic curve was 0.69. Therefore, there was no threshold early HbA1c value that predicted adverse pregnancy outcome with acceptable accuracy. Similarly, Starikov et al. [79] in his recent study found that early HbA1c does not predict adverse pregnancy outcome (preeclampsia, fetal growth restriction, abruption, preterm delivery PPROM), except for elevated HbA1c (>8.5 %) being associated with an increased risk of shoulder dystocia.

Antepartum Goals

Untreated maternal hyperglycemia alone or with the presence of maternal ketoacidosis can result in stillbirth. Therefore, maintaining maternal euglycemia is crucial before and during pregnancy to help prevent fetal anomalies. Currently, most experts recommend continued frequent glucose surveillance (4 to 7 times daily), maintenance of a stable diet, and adequate glycemic control (fasting glucose ≤95 mg/dL and postprandial glucose ≤120 mg/dL after 2 h or ≤140 mg/dL after 1 h). These goals can be achieved with the use of antidiabetic (hypoglycemic) medications (e.g., glyburide or metformin), insulin, or combination of both.

All women (except some with diet-controlled gestational diabetes) should undergo antenatal fetal testing. Antenatal testing has been shown to improve perinatal outcomes [80, 81]. Presently, most centers use either the biophysical profile (BPP) or the nonstress test (NST) with measurement of the amniotic fluid index (modified BPP). The timing and frequency of antenatal fetal surveillance varies between institutions and has been a subject of debate among experts; however, testing in most centers occurs twice per week from 32 to 34 weeks of gestation [80].

The screening and identification of macrosomia are also important aspects in the management of diabetic pregnant women. According to the American College of Obstetricians and Gynecologists [82], if the estimated fetal weight >4500 g, then cesarean delivery can be offered to these women to avoid birth trauma and birth asphyxia. Unfortunately, the currently used ultrasound fetal measurements are poor predictors of fetal macrosomia during late gestation with up to a 15 % error in estimation of fetal weight [83–85].

Timing of Delivery

This topic has always been controversial among experts. To date, few randomized trials have addressed the best time for delivery. The risk of stillbirth needs to be weighed against the risk of prematurity and RDS associated with early delivery. Recently, the American Congress of Obstetricians and Gynecologists (ACOG) published guidelines on timing the deliveries of diabetic pregnancies [86]. Women whose diabetes (both gestational and pregestational) is well-controlled can be delivered at 39 weeks. On the other hand, women with poorly controlled DM (gestational and pregestational) can be delivered at any time from 34 to 39 weeks. Unfortunately, the definition of "well-controlled" can vary among providers and is subject to individual interpretation. The range from 34 to 39 weeks is wide, and other individual factors (obesity, age, prior obstetrical history, concurrent medical or obstetric complications) must be taken into consideration when delivery is planned for a poorly controlled diabetic woman. Amniocentesis for fetal lung maturity was routinely performed prior to planned early delivery in diabetic women. The recent ACOG Committee Opinion [87•] states that, "for an early delivery, amniocentesis to confirm fetal lung maturity is no longer necessary." If there is an appropriate and accepted indication for delivery less than 39 weeks, then fetal lung maturity studies are not necessary for obstetric decision-making.

Hypoglycemia (Blood Sugar <45 mg/dL)

Just like hyperglycemia, hypoglycemia should be avoided during pregnancy. Women who require medical treatment for diabetes should not be overtreated. Measures such as frequent blood sugar monitoring, administration of ultra-rapid insulin and insulin pumps, frequent meals, and treatment of early symptoms of hypoglycemia can reduce the frequency of hypoglycemic episodes.

Other

Many studies show that fetal echocardiography should be routinely performed in women with pregestational diabetes. Many centers perform fetal echocardiography for the first time during the second trimester, preferably 18–22 weeks of gestation [88••, 89], to screen for congenital heart disease in the fetus and for the second time during the third trimester to screen for cardiomyopathy and heart failure. However, the efficacy of routine third trimester fetal echocardiography has not been proven.

Conclusions

Many questions on the mechanisms of stillbirth in diabetic pregnancies still currently remain unanswered. Perhaps better elucidating the pathways that lead to stillbirth will lead to the development of specific therapies. Currently, studies are underway to evaluate the safety profile for pravastatin (NCT01717586, ClinicalTrials.gov). Statins (FDA category X) are of particular interest to scientists, since they are well-known to counteract endothelial injury, oxidative stress, and pro-inflammatory pathways outside of pregnancy and in animal models. On the other hand, more novel medical treatments need to be developed to keep blood sugar levels within a normal range throughout pregnancy. Continuous glucose monitoring devices [90] have already been developed; however, they have not yet found their way into routine clinical practice. New and better antenatal tests also need to be developed to identify fetuses that are at highest risk for stillbirth. Finally, new algorithms that incorporate individual patient risk factors need to be developed that would guide the optimal timing of delivery for diabetic mothers who fail to achieve euglycemia during pregnancy and require early delivery to avoid stillbirth and reduce perinatal mortality.

Compliance with Ethics Guidelines

Conflict of Interest Roman Starikov, Donald Dudley, and Uma M. Reddy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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