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Review of Stillbirths among Antepartum Women with Gestational and Pre-Gestational Diabetes

Abstract

Background: The literature is replete with reports describing the effect of diabetes on pregnancy outcomes, particularly the risk of stillbirth. The goal of this review is to explore the relationship between maternal diabetes and fetal demise.

Aim: To review the risk of stillbirths in pregnancies complicated by Type 1, Type 2, and gestational Diabetes Mellitus.

Discussion: Type 1 diabetes mellitus (T1D), Type 2 diabetes mellitus (T2D), and gestational Diabetes Mellitus (GDM) identified during pregnancy have been independently associated with an increased risk of stillbirth compared to pregnancies not affected by these conditions. Published guidelines for prevention and management of GDM are lacking, but the existing evidence indicates that achieving glycemic targets during pre-conception is associated with decreased rates of stillbirth.

Conclusion: Diabetes is an independent risk factor for stillbirth that is amenable to achieving glycemic targets. Evidence-based recommendations for antenatal screening glycemic management are warranted to achieve reduction in stillbirth rates for gravidas with pre-gestational and gestational DM.

Keywords: Adverse outcome; Congenital malformations; Gestational diabetes; Diabetes; Maternal morbidity; Pre-gestational diabetes; Pregnancy; Perinatal mortality; Still births; Type 1 Diabetes; Type 2 Diabetes

Commentary

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Background

There has been extensive research into the effects of diabetes mellitus (DM) on pregnancy outcomes, and in particular on risk of stillbirth [1,2]. This article aims to bring together those studies to discuss the relationship between antepartum DM and stillbirth.

DM is an umbrella term for several different pathological conditions in which blood glucose is elevated, with a variety of etiologies. Type 1 diabetes mellitus (T1D) is caused an immune-mediated condition in which the beta cells of the pancreas are destroyed and thus unable to produce insulin [3]. Type 2 diabetes mellitus (T2D) is a condition in which the beta cells of the pancreas may have impaired function, but the primary defect is that of insulin resistance. There are numerous etiologies of this condition, including obesity, as well as secondary causes such as hemochromatosis and PCOS [2]. Gestational diabetes mellitus (GDM) is defined as DM associated with pregnancy. GDM is present in about 2-5% of pregnancies in the U.S. [2,4]. Due to current screening guidelines, GDM is generally not diagnosed until after 24 weeks of gestation [2]. Regardless of etiology, DM during the antepartum period is associated with the following risks to the fetus: neonatal death, preterm delivery, congenital anomalies, large for gestational age infants, shoulder dystocia, Erb's palsy, APGAR < 7 at 5 minutes, and admission to intensive care [5,6].

Stillbirth is generally defined as an intrauterine fetal death at 20 weeks or more gestation. According to an ACOG bulletin on managing stillbirth, published in 2009, 1 out of 160 births are stillborn [7]. Approximately, 26,000 fetal deaths at 20 weeks or more gestation were reported in the United States in 2006, which translates to 6.05 stillbirths per 1,000 births [8]. Many attempts have been made to classify causes of stillbirth, and known causes include unfavorable genetics, infection, fetal maternal hemorrhage, antiphospholipid syndrome, thrombophilias, and the subject of this review: diabetes mellitus [9].

Discussion

An audit on stillbirths among women with T1D in Denmark confirmed that suboptimal glycemic control, both pre-conception and antepartum, is associated with cases of stillbirth [10]. A similar study in Australia confirmed these findings, that pregestational, maternal T1D is associated with an increased risk of stillbirth [11]. A retrospective cohort study of 182 antepartum women with T2D showed a two-fold risk of stillbirth among affected women [12].

Less is known about the relationship of GDM with risk of stillbirth. T2D and GDM have similar pathophysiology, and thus some proven risk of stillbirth attributed to T2D may be extrapolated to GDM, but there is little evidence to support this. The underlying reasons for this lack of evidence are not clear, but a recent study by Hutcheon et al. [13], in which national data on GDM and stillbirth was re-categorized and then reanalyzed, the risk for stillbirth among women with GDM was significant [13]. Other studies have shown that, when compared to pregnancies not affected by DM, a diagnosis of DM during pregnancy portents a 4.5-fold risk of stillbirth [14].

The pathogenesis of high stillbirth rates among pregnancies complicated by diabetes is unknown, but likely to be multifactorial. One theory is that many cases are due to chronic hypoxia and associated acidosis. In addition, cardiac defects are not infrequently identified in infants born to women with T1D [15]. Schaefer-Graf et al. [16] reported that increased maternal hyperglycemia was associated with co-morbid fetal genetic syndromes and congenital abnormalities that are also independently associated with fetal death [16]. While congenital anomalies may be the cause of some stillbirths, these anomalies are not the only cause of stillbirth occurring in pregnancies affected by DM. A study by Tennant et al. [17] compared the risk of stillbirth for gravidas with pregestational diabetes with and without a congenitally anomalous fetus and found a 4.5 fold stillbirth risk even in the absence of fetal malformation [17].

As far as management of DM during pregnancy, in a meta-analysis of 70 studies on screening and management of diabetes during pregnancy, the only timing intervention associated with a significant decrease in rate of stillbirths rates occurred during the preconception period. That is, achieving glycemic targets prior to conception, as opposed to waiting until pregnancy confirmation or even later in pregnancy [18]. These results are particularly salient in light of the finding by Schaefer-Graf et al. [16] that elevated risk of congenital anomalies was associated with maternal hyperglycemia at the time of entry into prenatal care. This findings indicate that maternal hyperglycemia early on in pregnancy (e.g. prior to the time of entry into prenatal care) seems to be the root of the associated adverse perinatal outcome [16]. Thus, stillbirth appears to be a direct risk of maternal hyperglycemia, irrespective of the fact that maternal hyperglycemia is also associated with an increased risk of congenital anomalies, and in addition, congenital anomalies themselves are sometimes to blame for cases of stillbirth. In other words, among gravidas with DM, regardless of whether fetal anomalies are present or not, the risk of stillbirth exists [16,17].

The aforementioned meta-analysis by Syed et al. [18] also found a slightly greater reduction in risk of stillbirth when intensive diabetic control was instituted versus conventional control [18]. A randomized trial conducted to study the benefits of treating mild GDM versus providing only usual prenatal care found a lower rate of complications among the treated group; however, this study was not able to evaluate for stillbirth as an outcome [19]. Due to the fact that risk for stillbirth among antepartum women with any type of DM is elevated, as well as evidence that other studies on the topic failing to support this finding may have been flawed, recommendations to attempt strict glycemic control among antepartum women that include those with GDM is reasonable [20].

Glycemic control antepartum is a relatively contested topic. Findings that sub-optimally controlled hyperglycemia, in particular prior to conception, is associated with increased risk of stillbirth [10] are not generally based on large studies, and many studies do not examine GDM that occurs before 24 weeks due to the structure of screening for DM currently in place. An additional caveat to these findings is that the cases in which stillbirth occurred may have been due to hyperglycemia that was harder to control (for various pathophysiological reasons) versus suboptimal glycemic control due to a lack of intervention. More applied research is needed particularly in programming aimed at strict pre-conception glycemic control, even among women at risk of GDM, and not just those already diagnosed, to determine whether this would decrease risk of stillbirth among these women.

Additional considerations in management of antepartum women include optimal time of delivery, which was specifically assessed as part of a large, retrospective study comparing the risks of delivery to the risks of expectant management by gestational age among pregnancies affected by GDM. For both study groups, the risks of earlier delivery (at 36 weeks) were found to surpass the risks of expectant management. This risk-benefit ratio reversed at 38 weeks. In examining the study results further, based on number needed to treat analysis, the authors concluded that among women with GDM, the benefits of delivery exceed those of expectant management appreciably at 39 weeks and beyond, and thus planned delivery at 39 weeks is optimal for antepartum patients with GDM [21].

Evidence-based guidelines for antepartum management of DM vary situationally. Earlier studies showed that early delivery may be indicated in some patients with vasculopathy, nephropathy, unmet glycemic targets, or a prior stillbirth. In contrast, gravidas whose glycemic targets are achieved may be may be managed by obstetric indications, continuing to full term as appropriate by antenatal testing [22]. Recommendations to address this increased risk among antepartum women with DM, include increased frequency of prenatal care visits to ensure glycemic targets are met, as well as twice weekly reactive non-stress testing (NST) beginning in most cases between 32 and 34 weeks of gestation [23].

Conclusion

After a review of the current literature available regarding the risk of stillbirth among antepartum women with DM of any type, it is clear that the risks among this population are higher compared to women without this condition [9-15].

Prevention of the devastating outcome that is stillbirth is not relevant solely because of the severity of the outcome, but also because of the relatively high incidence. There appears to be a dearth of evidence confirming the timeline for when stillbirth is preventable, and much of the research that negates findings that managing DM reduces risk of stillbirth is based on interventions later in the antepartum period, which is likely too late. This is supported by the finding that pre-conception interventions where glycemic index was tightly controlled were associated with lower risk of stillbirth than cases where the intervention of tight glycemic control was not instituted until later on in pregnancy [16-18].

Potential opportunities to reduce the risk of stillbirth among antepartum women with DM include a focus on pre-conception glycemic targets, frequent fetal testing in the third trimester, and consideration of delivery at 39 weeks of gestation for women [18,21]. In addition, consideration of earlier screening among women at risk of GDM is worth revisiting. The U.S. Preventive Services Task Force (USPSTF) cites a lack of evidence to support earlier screening as the reason for not recommending it, rather

than evidence demonstrating that it is not actually useful in preventing negative fetal outcomes [24]. Thus, further research is needed in this area, to determine when screening for gestational diabetes would provide the optimal benefit.

Lastly, in terms of managing fetal monitoring during the antepartum period [25], the finding that normal results of once weekly non stress test (NST) beginning at 32-34 weeks of gestation do not preclude a stillbirth within 7 days among antepartum women with DM prompted the recommendation for twice weekly NST in these cases [23], which is well-supported. It is important, given the relative prevalence of DM during pregnancy, not to discount the potential severity of its effects.

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