

Unraveling the Mystery of Perinatal Deaths in Diabetic Pregnancy



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Introduction

Diabetes concurrent with pregnancy is a high risk condition and is associated with an increased risk of prenatal mortality. Stillbirth is defined as fetal death after 20 weeks of gestation. Other terms for stillbirths include fetal death, intrauterine fetal death, fetal demise, intrauterine fetal demise. Stillbirth rate is 4-6 times and neonatal mortality is 2-4 times higher in diabetic than in non-diabetic pregnancies. The term prenatal mortality rate is defined as the number of stillbirths after 20 weeks of gestation and number of infant deaths up to 28 days of life [1]. In the pre-insulin era successful pregnancy was rare in women with pregestational diabetes with prenatal mortality rate as high as 65% [2]. However with advent of self-monitoring of blood glucose by glucometers, HbA1c, continuous glucose monitoring, insulin pens, pumps, availability of newer insulin analogues, improved perinatal care, including fetal surveillance techniques, ultrasonography and Doppler, timely labor induction and advanced neonatal care the rate of fetal death in diabetic women has reduced substantially. This article outlines the incidence, path physiology and measures to reduce the risk of stillbirth in diabetic pregnancies.

Epidemiology of stillbirth in diabetic pregnancies

A number of studies have been done to evaluate the rate of stillbirth in the diabetic pregnancies. However the rate is mainly influenced by sample size in a specific study and hence many studies lack sufficient power. Monde stein and colleagues from United States reported a stillbirth rate of 5.9/1000 births in diabetic pregnancies and a stillbirth rate of 4/1000 births in non-diabetic populations, yielding a relative risk of 1.5 [3]. However in this study the diabetic population was not divided into pregestational type 1, type 2 and gestational diabetes. Studies analyzing stillbirth rate in type 1 pregestational diabetes have reported 3 to 5 times increased risk of stillbirth as compared

to non-diabetic population. In a study from Scotland (from 1979 to 1995) the incidence of stillbirth in women with type 1 diabetes was reported to be 25/1000 births and compared to the general population, the overall rate was 4.7 times higher [4]. Another study in United Kingdom reported 5 times higher rate of stillbirth in type 1 diabetics than the general population [5]. In a study from New Zealand it was observed that rate of fetal death was higher in type 2 diabetes than type 1 diabetes (34/1000 births versus 12/1000 births [6]. Another study by Clausen and colleagues reported a higher prenatal mortality rate in type2 diabetes than in type1 diabetes (67/1000 and 17/1000 respectively) [7]. This higher rate of fetal deaths in type 2 diabetes than in type 1 diabetes is attributed to higher incidence of obesity, hypertension and advanced maternal age in these patients. In GDM it has been observed that there is a positive relationship between levels of maternal average blood glucose levels and perinatal morbidity and mortalities Sullivan et al. [8] reported that women with GDM have more prenatal losses than pregnant non-diabetic women, 64/1000 versus 15/1000 respectively [8]. Schmidt et al. [9] comparing GDM women to the general population reported a relative risk of 3.1(95% CI 1.4 -6.5) for perinatal deaths [9].

Causes of perinatal mortality in diabetic pregnancy

In 1973 in a study of 187 women O' Sullivan & colleagues [8] reported higher perinatal mortality rate of 64/1000 births [8]. In another study White and Beischer reported perinatal mortality rate of 16/1000 births in women with GDM. According to this study the main reasons for the perinatal mortality were congenital anomalies, respiratory distress with prematurity and intrauterine hypoxia [10]. Stillbirth in diabetes is attributed to a number of causes, although approximately 50% are idiopathic. Stillbirth is caused by maternal, fetal or placental conditions, and

may be the result of the interactions between them. Commonly recognized causes of still-birth include fetal congenital abnormalities, fetal aneuploidy, placental abnormalities, placental insufficiency, fetal infection, polyhydramnios, premature rupture of membranes, preterm births, associated maternal hypertension, associated hypothyroidism, systemic maternal infection and sepsis, and autoimmune diseases like systemic lupus erythematosus, antiphospholipid syndrome. Congenital birth defect is one of the leading identifiable causes of intrauterine fetal death in women with pregestational diabetes [11]. High or uncontrolled blood glucose levels reflected as raised HbA1c in the first trimester increase the incidence of fetal birth defects particularly cardiovascular and neural tube defects. The term diabetic embryopathy stands for congenital malformations of infants of gestational diabetic mothers. Women with pregestational diabetes plus fasting hyperglycemia have 3 to 4 times greater risk of congenital malformations in their infants than the general population. Increase prevalence of malformation was 5.1% for an HbA1c of 7-8.5%, 22.9% for a level of 8.6-9.9%, and 21.7% for a level of HbA1c above 10%. Even a slightly raised level of HbA1c during early pregnancy in woman with type 1 diabetes is associated with an increased risk of fetal malformations. Cardiovascular and atrioventricular discordance, outflow-tract anomalies associated with normally related great arteries and complete forms of atrioventricular septal defects. The VACTERL cluster includes Vertebral anomalies, Anal atresia, Cardiac defect, Tracheo-Esophageal fistula, Renal abnormalities and Limb abnormalities [12]. In diabetic pregnancy caudal (sacral) agenesis, which accounts for <5% of major anomalies occurs ~50 times more often during pregnancy in women with DM than in women without DM [13]. Almost half of the stillbirths in pregestational diabetic pregnancies occur before 30 weeks of pregnancy. Maternal obesity, higher maternal age, poverty, and hyperglycemia are risk factors for late intrauterine deaths. In women with prepregnancy body mass index (BMI) >30kg/m² the risk of stillbirth and neonatal death is doubled [14]. Chances of stillbirth increases in fetuses that are having birth weight 4000g both in diabetic and non-diabetic pregnancies. Macrosomia is defined as birth weight in excess of 4000-5000g or infants with large gestational age. Fetal macrosomia is 10 times more common in diabetic women than in non-diabetic women. In the fetus of diabetic mother excessive growth may cause shoulder dystocia, traumatic birth injury and asphyxia. Late fetal deaths in diabetic pregnancies are related to chronic intrauterine hypoxia. It has been observed that iron stores in the liver, heart and brain are significantly depleted in most fetuses that die after 35 weeks of gestation [15]. Which indicates that fetal death is preceded by a period of chronic hypoxia? Fetal serum and stored iron is used for red cell production during a prolonged period of hypoxia. Stillborn infants of diabetic mothers have relatively heavier hearts than stillborn infants of non-diabetic mothers [16,17]. Which probably also reflects chronic fetal hypoxia in pregnancies complicated by maternal diabetes.

Pathophysiology of perinatal mortality

The cause of fetal death in women who have pregestational diabetes is not clear. Historically the pathophysiology for the deaths has been attributed to undetected hyperglycemia and ketoacidosis [18]. Past reports have noted perinatal mortality death rates of 50% to 90% in women in ketoacidosis. Hyperglycemia and poor glucose control have been postulated to be the underlying cause of approximately half of all fetal deaths. Fetuses of diabetic mothers with poor glycemic control are chronically hyperinsulinemic. Fetal hyperinsulinemia increases fetal metabolic rate and oxygen requirements of fetus. Fetal hyperglycemia and hyperinsulinemia can cause fetal hypoxia which may lead to fetal death. Sudden rise in amniotic fluid erythropoietin level is an indication of fetal hypoxia in diabetic pregnancy. Fetal erythropoietin concentrations directly correlate with maternal HbA1c levels. Therefore during pregnancy it is important to maintain the glycemic level within normal. A decrease in umbilical and placental blood flow is seen due to fetal hyperinsulinemia. This cause the worsening of fetal hypoxia. Both ante partum and intrapartum abnormal fetal heart rate (FHR) changes are increased and cord blood acidosis and low Apgar scores are considerably more common in diabetic than in non-diabetic pregnancies which indicates that fetal hypoxia complicates these pregnancies. Neonatal polycythaemia and increased number of nucleated red cells in cord blood occur frequently in pregestational diabetic pregnancies which are the indicators of fetal hypoxia. Other factors such as preeclampsia and maternal vasculopathy can also contribute to reduced placental blood flow and fetal oxygenation. Studies of fetal umbilical cord blood samples in pregnant women with type 1 diabetes have revealed lactic acidemia. Maternal diabetes may also produce alterations in red blood cell oxygen release and placental blood flow. Reduced uterine blood flow contributes to increased incidence of intrauterine growth restriction observed in pregnancies complicated by diabetic vasculopathy.

Strategies for prevention of stillbirth in diabetic women

In women with pregestational diabetes, comprehensive multidisciplinary care is required for improving the pregnancy outcome. A multidisciplinary team consisting of an obstetrician, a physician/endocrinologist, neonatologist dietician and physical instructor should be involved in the management of a diabetic pregnancy. Preconception counseling is essential along with close supervision of a diabetic pregnancy with an aim to keep HbA1C <6%. Since most complications in diabetic pregnancy are related, directly or indirectly to maternal hyperglycemia and fetal hyperinsulinemia it is obvious that therapeutic strategies should be directed towards normalization of maternal blood glucose levels. To achieve aggressive blood sugar control intensive insulin therapy in the form of multiple doses should be considered. Reducing extremes in blood sugar

readings is an important tool to reduce the risk of stillbirth. Insulin therapy should be individualized with dosage tailored according to diet, exercise and glycaemic status. Diet therapy is critical to successful regulation of maternal blood glucose levels. A programmer consisting of three meals and three snacks is employed for most patients.

Antepartum fetal evaluation

Antepartum fetal monitoring plays an important role in reducing the risk of stillbirths in diabetic pregnancies. In each visit, fundal height, abdominal girth and fetal heart determination should be done to evaluate fetal growth. Serial clinical evaluation of daily fetal movement count: Maternal assessment of fetal activity serves as a simple and cost effective screening method for fetal surveillance. During the third trimester, women are instructed to perform daily fetal movement count. Its role in reducing still births is not conclusive, yet it's a simple and noninvasive method. Non stress test: It is the preferred primary method to assess fetal well-being. A reactive non stress test is reassuring and over 99% of cases are expected to survive over the next seven days. In diabetic pregnancies NST testing is generally started after 32 weeks, 1-2 times a week. In patients with vascular disease and poor control, in whom the incidence of abnormal tests and intrauterine death is greater, testing is may be started between 28 and 32 weeks' gestation. In addition to NST, biophysical scoring is done to assess fetal wellbeing by assessing fetal heart reactivity, fetal tone, fetal gross body movements, fetal breathing and amniotic fluid index. Doppler velocimetry of fetal vessels is also useful in predicting adverse outcomes. Ultrasound is useful for evaluating fetal growth, estimating fetal weight, detecting hydramnios and malformations. Biochemical testing may be done in the first and second trimester along with a detailed anomaly scan at 18 weeks to detect neural tube defects and other anomalies. Fetal echocardiography is performed at 20 to 22 weeks' gestation for the investigation of possible cardiac anomalies.

Timing of delivery

The optimum timing of delivery remains unclear but the goal is to delay delivery to minimize risks of respiratory distress/hyaline membrane disease of the newborn on one hand and deliver early enough to avoid significant risks for fetal loss on the other hand. In GDM controlled on diet, fetal testing is initiated in the 3rd trimester and delivery is planned at 40 weeks. In patients who require insulin without risk factors for adverse outcomes (vasculopathy, hydramnios and macrosomia), delivery should be planned at 38 weeks. The women who have estimated fetal weights of 4500g should be delivered by cesarean section. Before an elective cesarean section, steroid injections should be administered to the mother for ensuring fetal lung maturity. In women with poor glycaemic control and in presence of other complications, delivery may be planned earlier in view of increasing risks for fetal demise in this population.

Conclusion

Perinatal deaths occur with increased frequency among pregnancies in diabetic mothers. There is a strong association between the rate of stillbirth and maternal hyperglycemia. The rate of stillbirths has reduced steadily with improvements in diabetic control and improved fetal surveillance during pregnancy. With the use of SMBG, diet, physical exercise, insulin and a multispeciality team approach it is possible to achieve euglycemia in diabetic patients which will reduce associated perinatal morbidity and mortality.

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