Intrauterine fetal demise with caudal regression syndrome, a case report

Devin McKissic BS,[1] Colleen K. Stockdale MD, MS[2]

Key words: Intrauterine fetal demise, caudal regression syndrome, diabetes mellitus

Abstract

Background: The causes of intrauterine fetal demise are varied and not entirely well-understood. Multiple observational studies have shown that both perinatal and infant mortality rates are increased in children of diabetic mothers when compared to those of nondiabetic mothers.

Case: We present a case involving a 22-year-old G4P0120 with poorly controlled type 1 diabetes mellitus and a complex medical history including two first trimester fetal losses, and second trimester intrauterine fetal demise who presented during the second trimester for care and was found to have a fetus with ultrasound findings consistent with caudal regression syndrome. When she presented in labor at term intrauterine fetal demise was identified.

Discussion: Infants and fetuses of diabetic mothers are at a higher risk for congenital anomalies, one of which is the potentially devastating caudal regression syndrome. However, it appears that this risk may be lowered with strict glycemic control both before and during pregnancy.

[1]*University of Iowa Carver College of Medicine, Iowa City, Iowa*
[2]*University of Iowa Hospitals and Clinics, Department of Obstetrics and Gynecology, Iowa City, Iowa*

Introduction

Fetal death, though relatively more prevalent in low- and middle-income countries, remains an issue in the United States with a fetal mortality rate (defined as fetal death at >20 weeks gestation) of 5.96 of 1000 live births and fetal deaths.[1,2] Several risk factors for fetal death and stillbirth have been identified that allow practitioners to identify which patients may be at greater risk for these outcomes. Unmodifiable risk factors include nulliparity or multiparity ≤3, African, African-Caribbean, Indian and Pakistani ethnicity, maternal history of mental health problems, and antepartum hemorrhage. Potentially modifiable risk

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Corresponding author: *Colleen Stockdale, MD, MS, Department of Obstetrics and Gynecology, 200 Hawkins Drive, Iowa City, IA 52246, Phone: 319-384-6849, Fax: 319-384-8620. Email: colleen-stockdale@uiowa.edu*

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factors include smoking, maternal obesity, fetal growth restriction, and pre-existing maternal diabetes.[3]

The causes of fetal death are varied and not entirely well-understood. Identified causes include placental, fetal, and maternal abnormalities, but a significant percentage of fetal death remains idiopathic. Placental pathologies that may lead to fetal death include placental bed abnormalities (e.g. abruptio placentae), placental developmental abnormalities (e.g. placental hypoplasia), placental parenchyma abnormalities (e.g. fetal thrombotic vasculopathy), and umbilical cord abnormalities (e.g. knots, strangulation).[4] Fetal abnormalities may be genetic, such as trisomy 18, or structural, such as spina bifida. Finally, maternal abnormalities leading to fetal death include systemic syndromes such as preeclampsia or diabetes as well as infection.[5]

The fetuses and infants of women with diabetes are subject to higher rates of complications when compared to their counterparts with nondiabetic mothers. Multiple observational studies have shown that both perinatal and infant mortality rates are increased in children of diabetic mothers (particularly those with preexisting diabetes) when compared to those of nondiabetic mothers. Though complicated deliveries (as evidenced by higher levels of Caesarean sections and forceps or vacuum-assisted vaginal deliveries in diabetic women) likely contribute to this observation, the increased incidence of congenital anomalies in these fetuses and infants may have an even greater impact.[6-10]

Case Report

A 22-year-old G4P0120 with poorly controlled type 1 diabetes mellitus and a complex medical history including two first trimester losses, and recent induction of labor for a second trimester loss following presentation at 28 weeks with ultrasound revealing fetus at 20 3/7 weeks with signs of significant fetal decomposition, presented for initial care at 26 1/7 weeks gestation. The dating ultrasound revealed a fetus with no lumbar or sacral spine, consistent with caudal regression syndrome (CRS). Medical history was significant for diabetes mellitus (diagnosed at 4 years of age) with multiple hospitalizations for diabetic complications, tobacco dependence, and subsequent urine drug screen positive for amphetamines at her 35 week antenatal visit.

Following the previous second trimester intrauterine fetal demise (IUFD) the patient underwent a comprehensive workup for antiphospholipid antibody syndrome and other thrombophilias, thyroid derangements, fetal hemorrhage, and infections including: cytomegalovirus, herpes simplex virus, parvovirus B19, and toxoplasmosis which was negative. Placental analysis by pathology showed a two-vessel umbilical cord, chorioamnionitis, amnion nodosum, mild increase in intervillous fibrin and microcalcifications. The patient denied fetal autopsy, and the IUFD was felt to be the result of poorly controlled maternal diabetes.

The patient presented to labor and delivery at 38 4/7weeks gestation with increasing contractions and decreased fetal movement. Fetal heart tones were absent on arrival and term IUFD was

confirmed via ultrasound. Initial laboratory results were remarkable for blood sugar 210 mg/dL and elevated beta-hydroxybutyrate at 1.6 mmol/L (reference range less than 0.4-0.5 mmol/L), with an anion gap of 18 mEq/L (reference range 3-11 mEq/L). Fluids and insulin were administered and a repeat beta-hydroxybutyrate was <0.1 mmol/L.

Labor and delivery were complicated by artificial rupture of membranes yielding thick, malodorous fluid, maternal fever to 38.0° consistent with chorioamnionitis requiring ampicillin and gentamicin, and shoulder dystocia. Delivery yielded a highly edematous fetus with small, bowed, and contracted lower extremities. Repeat IUFD workup for antiphospholipid antibody syndrome and thrombophilias, fetal hemorrhage, and thyroid derangements was normal. Placental analysis by pathology showed a two-vessel umbilical cord, acute chorionitis, and third trimester chorionic villi. She again declined fetal autopsy; the cause of the term IUFD was attributed to caudal regression syndrome in the setting of maternal diabetes.

Discussion

Fetal death can be a highly emotional event, which may make searching for and determining an etiology difficult. The American College of Obstetricians and Gynecologists (ACOG) recommends a thorough evaluation, including placental and umbilical cord examination, genetic analysis of the fetus, maternal screening for infection, lupus, and thyroid problems, and an autopsy if the family permits.[11]

Women with diabetes may have pregnancies complicated by a variety of congenital anomalies, with cardiac anomalies being the most common. Anomalies of the musculoskeletal system, central nervous system, genitourinary system, and ear, nose, and throat may also be seen.[6, 7] No anomaly appears to be pathognomonic for infants of mothers with diabetes; however, the anomaly that comes closest, with a relative risk of 200-400, is CRS.[6] Yet many cases of CRS occur in fetuses and infants whose mothers do not have diabetes, with approximately 22% of CRS cases occurring with diabetic mothers.[12]

Caudal regression syndrome was first described by Duhamel in 1961.[13] It is characterized by varying levels of sacrococcygeal or lumbosacrococcygeal agenesis, which may be accompanied by abnormalities or hypoplasia of the pelvis and legs.[14] The diagnosis of CRS may be made early in gestation with sonographic recognition of a decreased crown-rump length. Later, sonographic evaluation will yield evidence of a shortened spine with deficits in the lumbar and sacral regions, short femora, and flexion contractures of the lower extremities.[15] If diagnostic uncertainty remains, or further evaluation is necessary, amnioinfusion or MRI may be helpful to better visualize fetal structures.[14, 16]

In addition to the classic “frog-leg” presentation due to the flexion contractures of the lower extremities,[12] CRS has also been associated with abnormalities of the urinary tract, genitalia, and anorectal area. One particular constellation of such abnormalities is known as the OEIS

complex: omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects.[14, 17]

The prognosis for infants with CRS is variable, and somewhat dependent upon the degree of sacral agenesis. Infants with complete sacral agenesis are at a higher risk for complications and early neonatal death. All will need a thorough evaluation after birth by urology and orthopedics, as well as for any other anomalies they may have. Those who survive past infancy tend to have long term problems due to neurogenic vesicopathy and neuromuscular deficits in the lower extremities.[16]

The pathogenesis of CRS is poorly understood. It likely arises from an issue with the gastrulation process leading to a defect in the mesoderm and induction of caudal elements in the embryo before the 4th week of gestation.[12, 14] Several gene/protein pathways, including the Shh, Cdx2, Acd, and Lrp6 pathways appear to be involved.[14] It has also been suggested that in mothers with diabetes, hyperglycemia leads to decreased myoinositol intake in the embryo, which in turn may cause abnormal fusion and folding events in the embryo.[12] It is likely that the pathogenesis of CRS is multifactorial, with both genetic and environmental components.

Though the infants of diabetic mothers do tend to have higher rates of anomalies, they are not doomed to this fate. Multiple studies have shown that while mothers with higher glycated hemoglobin levels early in pregnancy have higher rates of fetal anomalies, tight glycemic control both before and throughout the pregnancy may decrease these rates.[18-21] Therefore, pregnant women with diabetes should be counseled extensively about the benefits of maintaining good control of their diabetes.

Conclusion

Infants and fetuses of diabetic mothers are at a higher risk for congenital anomalies, one of which is the potentially devastating caudal regression syndrome. However, it appears that this risk may be lowered with strict glycemic control both before and during pregnancy. While the vast majority of healthcare providers encourage tight glycemic control in their pregnant patients with diabetes, efforts should be made to find ways to improve patient compliance in order to reduce the incidence of CRS and other diabetic complications.

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