Case Report

Title:

Relation between possible under-diagnosed/treated glucose dysmetabolism, delayed villous maturation, and lethal fetal pneumonia.

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Abstract

BACKGROUND: Gestational diabetes mellitus (GDM) is a known risk factor for stillbirth[1]. Delayed villous maturation (DVM), predominantly seen in term placentas in pregnancies complicated with glucose dysmetabolism, may in part be a consequence of excessive maternal glucose leading to release of fetal insulin and other growth factors that promote excessive placental growth at the expense of villous maturation[2].

CASES: We present three cases of under-diagnosed/treated glucose dysmetabolism in women in their first pregnancies cared for in other hospitals in the United Kingdom (UK) with the fatal fetal/neonatal outcomes and confirmed DVM in the placenta and congenital pneumonia on post-mortem examination in all three cases.

CONCLUSION: This cluster supports a hypothesis that DVM and glucose dysmentabolism may make babies more susceptible to severe perinatal infection. All three cases received the antenatal care in their subsequent pregnancies in our unit and had confirmed glucose dysmetabolism which was treated and resulted in healthy babies.

Introduction

Delayed villous maturation (DVM) and distal villous immaturity (DVI) terms were introduced in 2004 to describe an abnormally immature placental phenotype[2,3]. This has previously been described by Driscoll in a review of fetoplacental pathology in diabetic pregnancies[2,4]. Most cases occur at or near term and the prevalence in this gestational age range submitted to pathology is approximately 1-2% (unpublished data)[2,5].

Placental growth normally plateaus after 37 weeks due to a transition from new villous growth to terminal (distal) villous differentiation. Increased levels of placental growth factors in diabetes due to fetal hyperinsulinemia, and an excessive supply of nutrients may inhibit distal villous differentiation[2].

Fetuses whose placentas show DVM/DVI are considered to have a decreased reserve to withstand stressors such as transient hypoxia in the late third trimester and intrapartum period. Pregnancies affected by DVM/DVI may be unusually sensitive to acute episodes during which fetal demand exceeds placental supply, unlike maternal malperfusion where the fetus and placenta may become chronically adapted to hypoxia. Evidence includes the increased prevalence of DVM/DVI amongst stillbirths[2].

Herein, we present three cases of lethal infant outcome at term in three pregnant women with confirmed DVM/DVI on post-mortem examination. These patients had been self-referred to our team at University College London Hospital (UCLH) in their subsequent pregnancy after the index one(s). They were closely followed up from the beginning of the pregnancy by the Perinatal History Clinic, which was set up to reduce the incidence of adverse perinatal outcomes and specifically perinatal death. At the time of this submission, all three had already had a successful outcome in the subsequent pregnancy. The subsequent pregnancies were closely followed with careful glucose monitoring. Although the glucose tolerance test (GTT) result was within the normal range in the first two cases, there was evidence of reactive hypoglycaemia at 120 minute in both cases indicating the insulin resistance. Hence, we decided to treat the patients as per gestational diabetes protocol and delivered by planned caesarean section between 36 and 37 weeks' gestation. The third woman had confirmed gestational diabetes in her subsequent pregnancy, initially diet-controlled, then treated with medications, and she delivered by planned caesarean section just before 38 weeks ' gestation.

A retrospective review of the cases complicated with stillbirth before they were self-referred to our unit, with their consent and permission, follows.

Case 1

This was a thirty-two years old primigravida, with own-egg in vitro fertilisation (IVF), history of polycystic ovarian syndrome (PCOS), and ovarian hyperstimulation syndrome (OHSS) at the beginning of pregnancy. She had low risk combined first trimester screening test and normal fetal anomaly scan (scan between 19-24 weeks' gestation), with abdominal circumference (AC) on the 80th centile. At routine midwife appointment at 39+4 weeks' gestation urine was sent for microbiology investigation due to leucocytes presence in a urine dipstick, and Enterococcus spp was confirmed. Then she presented to the maternity assessment unit at 40+0 weeks' gestation with a first episode of reduced fetal movements lasting less than 10 hours. Fetal death and oligohydramnios were diagnosed. There was no history of spontaneous rupture of membranes, pyrexia, or vaginal bleeding. The baby was delivered the following day by caesarean section, on maternal request.

Blood tests results on the day of delivery, prior to caesarean section were consistent with infection and with borderline glucose dysmetabolism: haemoglobin (Hb) 102g/L, white cell count (WCC) 26.9 x 10^9/L, platelets (Plt) 396 x 10^9/L, neutrophils (Ne) 21.5 x 10^9/L, HbA1c 5.8% and 40 mM/M (ref 4.0-5.9% and 20-41mM/M respectively). Other results included a Rhesus positive blood group with no antibodies, Kleihauer-Betke test for feto-maternal haemorrhage negative at <4ml, negative IgG and IgM anticardiolipin antibodies and antinuclear antibodies, negative urine cultures on the day of caesarean section and Day 5 post delivery, negative blood cultures, and negative placental and high vaginal swabs for pathogens. Post-mortem examination reported in-utero fetal pneumonia and placental DVM/DVI and acute chorioamnionitis.

CASE 2

This was a thirty-one years old primigravida, with spontaneous conception, relatively late booking for antenatal care, a dating scan at 14+3 weeks' gestation, and a low risk quadruple test result. Fetal anomaly scan was completed at 22+4 weeks' gestation and no abnormality was detected. Body Mass Index (BMI) >35 indicated serial fetal growth scans at 28-32-36 weeks' gestation age (GA) and GTT at 27+6 GA. All the results were reported within the normal range. The estimated fetal weight (EFW) on the last scan at 36+3 weeks' gestation was above the 90th centile, and described in the maternity notes as "just below 95th centile".

There were three episodes of reduced fetal movements in the third trimester of pregnancy: The first episode was at 29 weeks' gestation, maternal observations and fetal cardiotocography (CTG) were normal, and she was discharged home. The second episode was at 38+6 weeks' gestation, when she presented with a history of reduced fetal movements for 24 hours. A computerised CTG was performed and Dawes-Redman criteria were met, and they were discharged home with a plan for weekly CTG monitoring, sweep of the cervix at 39+3 weeks' and induction of labour (IOL) at 40+0 weeks' gestation. The latest presentation with reduced fetal movements was at 40+0 GA and the induction of labour was commenced.

At 40+3 weeks' gestation induction was abandoned due failure to progress. In view of the normal investigations including the CTG, discharge from hospital was agreed at that point with a follow up appointment for CTG monitoring planned at 40+6 GA.

The woman attended the maternity assessment unit at 40+5 weeks' gestation in confirmed early labour. At 40+6 weeks' gestation, following no significant progress on vaginal examination and normal CTG, Pethidine 100mg IM was administered. 90 minutes later the fetal bradycardia of <60 beats per minute was auscultated, followed by emergency caesarean section delivery under general anaesthesia 24 minutes later. The Apgar scores were reported as 2 at 1^{st} minute and 5 at 5^{th} minute, and the cord blood gases - arterial pH 6.97, base deficit 11.8, venous pH 7.3, base deficit 5.9. The baby died on Day 6 of life. Post-mortem examination showed neonatal pneumonia and cardiomyopathy, placental DVM/DVI and acute chorioamnionitis.

CASE 3

This was a thirty-nine years old woman in her first pregnancy, with uncomplicated antenatal care, apart from the diet-controlled gestational diabetes diagnosed in 2^{nd} trimester. Although the access to her medical records was limited by the caring hospital, the first trimester screening test, fetal anomaly scan and growth scans were all with no abnormality detected.

Woman attended the maternity assessment unit at 40+4 weeks' gestation, just a day before the planned induction of labour, with a three-day history of reduced fetal movements. During the assessment, prolonged fetal bradycardia occurred. Although the emergency caesarean section was performed within 21 minutes after the bradycardia was declared the baby was stillborn. Thick meconium was noted at the time of caesarean section, but there was no cord around the fetal neck nor evidence of any retroplacental clot. Post-mortem examination showed placental DVM/DVI, acute chorioamnionitis and signs of fetal pneumonia.

DISCUSSION

Three cases of possible under-diagnosed and under-treated glucose dysmetabolism superimposed with choriamnionitis leading to lethal fetal/neonatal outcome and confirmed placental DVM/DVI and congenital pneumonia are described. In the first case, a primigravid woman with history of PCOS, IVF and OHSS, GTT was not performed. In the second case, GTT was performed at 27+6 weeks' gestation only, and it was not repeated later in the pregnancy despite the evident fetal growth at 95th centile at 36 weeks' ultrasound examination. In the third case, the gestational diabetes was diagnosed and controlled with diet, in line with that hospital local protocols, which had likely failed to optimise glucose levels and led to DVM/DVI. In their subsequent pregnancies, all three women had antenatal care in our unit, with close monitoring in Perinatal History Clinic. The glucose dysmetabolism was confirmed in all three cases: the first two women had gestational reactive hypoglycemia and the third woman had GDM requiring medications.

In the first case at 39+4 weeks' gestation Enterococcus spp was confirmed in urine specimen, followed by negative urine cultures on the day of caesarean section and Day 5 post delivery. Enterococcus spp may have been responsible the development of acute chorioamnionitis through ascendance in the amniotic cavity[13]. In the other two cases there was no significant maternal infection confirmed, neither by deteriorating maternal signs and symptoms nor by microbiology, but the diagnostic accuracy of clinical chorioamniotis is only 50%[14]. The third case was complicated with thick meconium which is associated with acute choriamnionitis[15-17] and increases the risk of fetal aspiration and the development of congenital pneumonia. Late chorioamnionitis is associated with poor neonatal outcomes including sepsis[18].

The relationship between respiratory distress syndrome (RDS) and GDM is well-documented[19]. A retrospective study of 200,000 term pregnancies identified a 1.5 and 3.1 times higher risk of RDS in women with GDM and pregestational diabetes[20]. GDM is often associated with higher rates of neonatal sepsis, altered immune function and neonatal infections[21-23]. A similar link may also exist between glucose dysmetabolism in pregnancy and acute choriamnionitis.

What was common across all three cases was the DVM/DVI, an infection which should not have been lethal, and the baby's death. There is a confirmed relation between diabetes in pregnancy with DVM/DVI; and DVM/DVI have been associated with fetal demise [24-25]. A study on 993 placentas with DVM/DVI identified 2.3% were associated with stillbirth. Although the incidence may seem low, the relative risk of death was 70 times higher than in fetuses with normal placentas[26]. While in a normal pregnancy the structure of chorionic villi ensures nutrient and oxygen delivery to the fetus, this exchange is compromised in case of villous immaturity leading to fetal hypoxia and subsequent death. As DVM/DVI is associated with glucose dysmetabolism, it poses the question whether more should be done to detect and treat it antenatally.

There is a significant variation in screening and diagnosis of glucose dysmetabolism in pregnancy[5] in the UK. The National Institute for Health and Care Excellence (NICE) recommends a 75g 2-hour GTT in women with risk factors (BMI>30kg/m^2, previous macrosomic baby weighing 4.5kg or more, previous gestational diabetes, family history of diabetes, or an ethnicity with a high prevalence of diabetes) between 24 and 28 weeks' gestation. A fasting glucose level of 5.6 mmol/l or above **or** a 2-hour glucose level of 7.8 mmol/l or above are current thresholds for diagnosis[6]. However, concerns remain that NICE thresholds underdiagnose those with glucose dysmetabolism in pregnancy (e.g. in women with PCOS, OHSS, age over 35) who may be at risk of adverse pregnancy outcomes[7-12], including women with DVM/DVI[27].

Women with known diabetes during pregnancy are at higher risk of stillbirth, and histopathology reports in 1-2% of the cases show DVM/DVI. Insulin resistance in pregnancies without confirmed GDM can also result in stillbirth with placenta histopathology confirming DVM/DVI. Whereas it is known that DVM/DVI may harm babies in utero by making them more susceptible to hypoxic insults, this cluster supports a hypothesis that DVM/DVI and under-diagnosed/treated glucose dysmentabolism may result in fatal fetal/neonatal outcomes.

This report has several limitations. Firstly, more cases are required to derive a significant conclusions (although we are aware of a further two cases, these could not be presented for legal considerations). Secondly, other factors might have contributed to the poor pregnancy outcome. In the reviewed available medical records (the access was limited to information provided by other hospitals where antenatal/intrapartum care in index pregnancies has taken place), the presence of meconium was not documented in in the first two cases, and there was no comment on meconium aspiration in the accessed histopathology report for the third case. However, all three cases did have proven DVM/DVI on histopathology examination.

The aim of this report is to raise the awareness on diagnosing and appropriately treating glucose dysmetabolism in pregnancy rather than GDM exclusively in order to prevent the perinatal deaths.

CONCLUSION

Poor outcome is described in all three index pregnancies, and specifically lethal fetal and neonatal pneumonia as a possible consequence of glucose dysmetabolism and DVM/DVI with superimposed acute chorioamnionitis. Further research is needed to elucidate the underlying pathophysiology of glucose dysmetabolism, DVM/DVI and transplacental immunity.

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Conflicts of interest: none declared

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The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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