case report

Placental steroid sulphatase deficiency: an approach to antenatal care and delivery

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Placental steroid sulphatase deficiency (SSD) is an X-linked inborn error of metabolism. Congenital X-linked ichthyosis (XLI) is a genetic disorder of keratinisation caused by steroid sulphatase (STS) deficiency, which results in a scaling skin condition in male infants shortly after birth. It may be associated with failed induction of labor and prolonged labor leading to cesarean delivery due to 'cervical dystocia'. We present two cases of congenital ichthyosis. Thorough counselling of women with a previously affected pregnancy during the antenatal period should include discussion about mode of delivery and a critical review of the complexities of prenatal diagnosis in this condition. We propose a clinical management pathway to offer women with a previous pregnancy affected by this rare condition.

SIMILAR CASES PUBLISHED: Less than 50 cases reported.

Placental steroid sulphatase deficiency (SSD) is an X-linked inborn error of metabolism.[1] It is associated with low estrogen production during fetal life. Congenital X-linked ichthyosis (XLI) is a clinically mild genetic disorder of keratinization,[2] which causes a scaling skin condition in male infants shortly after birth caused by the steroid sulphatase (STS) deficiency. It was initially identified as an enzyme disorder of the placenta, and referred to as placental SSD. The clinical importance lies in differentiating this disorder from other fetal defects that result in low estrogen concentrations during the antenatal period, which may well have different clinical outcomes and need different antenatal monitoring. Due to the low estrogen levels, these pregnancies may be prolonged, with dysfunctional labor that may end in cesarean delivery.

We present two cases of congenital XLI seen at our center. The emphasis is on presentation, diagnosis and management. In 2012, two women with a previous child affected by congenital ichthyosis booked at our high-risk antenatal clinic at the obstetric unit of Sunderland Royal Hospital, Sunderland, United Kingdom.

CASE 1

A 40-year-old woman had been seen at our clinic in 1992 during her first pregnancy, which ended in stillbirth at 28 weeks gestation at a neighbouring hospital. The female fetus weighed 700 g and the cause of death was recorded as 'placental insufficiency'. During her second pregnancy in 2009, at the age of 37 years, the patient underwent screening for Down's syndrome and incidentally was found to have a low serum estriol of 0.05 nmol/L. She underwent amniocentesis, due to a high risk result

which confirmed a male fetus with a normal 46,XY karyotype and an STS deletion on the short arm of the X-chromosome. Both parents underwent genetic testing and the mother was found to be a carrier of XLI. A uterine artery Doppler assessment performed at 23 weeks gestation was normal. Growth scans were also within the normal range. At 32 weeks gestation, she had spontaneous preterm rupture of membranes and was managed conservatively with close outpatient feto-maternal monitoring. She underwent induction of labor at 37 weeks gestation because of the previous stillbirth and prolonged ruptured membranes. She was given dinoprostone 3 mg per vagina followed by a 'syntocinon' infusion. She had slow progress of labor up to 9 cm cervical dilatation at which point cardiotocography (CTG) showed some potential signs of fetal compromise. At this point, she has had a total dose 4740 mU of syntocinon over 6 hours at an initial rate 2 mU/min which was increased every 30 minutes to a maximum infusion rate of 20 mU/min. An emergency cesarean delivery had to be performed for suspected fetal compromise based on the CTG changes.

During her third pregnancy in 2012, aged 40 years, the patient had Down's syndrome screening again and the serum estriol levels were found to be normal. However, she requested amniocentesis because of her anxieties related to maternal age, which confirmed a female fetus with a normal 46,XX karyotype and no deletion to suggest STS deficiency. Antenatally, she was offered vaginal birth after cesarean (VBAC). However, at 29+4 weeks gestation, she developed severe pre-eclampsia/HELLP syndrome and was delivered by emergency cesarean section.

CASE 2

A 32-year-old woman presented to our center during her first pregnancy in 2004. She had an uneventful antenatal period and did not undergo Down's syndrome screening. She went into spontaneous labor at 40+7 weeks and at 6-cm cervical dilatation, syntocinon infusion was commenced at a rate 2 mU/minute. This was increased every 30 minutes to a maximum infusion rate of 28 mU/min. She required an emergency cesarean delivery for 'failure to progress' with secondary arrest at 9-cm cervical dilatation. The total dose of syntocinon was 7860 mU over 8 hours. A live male infant was delivered in good condition. He was diagnosed in infancy with XLI after developing a scaling skin disorder a few months after birth. During her second pregnancy, she booked at our high-risk antenatal clinic. She had a normal anomaly scan at 20 weeks where a female fetus was identified, therefore excluding XLI. She was offered a trial of VBAC, which she accepted. However, at 2-cm cervical dilatation there was suspected uterine scar dehiscence based on acute CTG changes and she underwent emergency cesarean delivery. The baby was delivered in good condition with no uterine scar dehiscence or retroplacental clot.

DISCUSSION

X-linked ichthyosis (XLI) has a reported incidence of 1:2000-6000 male births.[3] It has no racial predisposition. It may be apparent at birth or in early infancy, but may not become evident until the child grows older. Clinicians will be unaware in the majority of primary pregnancies affected by placental SSD, as they follow a normal antenatal course and diagnosis is confirmed when the child develops XLI in later life. Obstetricians will become aware (as in these cases) when the previous history is apparent in subsequent pregnancies. It has been estimated that as many as one in 3000 pregnancies are affected.[4]

The first case of placental SSD was reported by France and Liggins in 1969.[5] At the time, it was thought to be extremely rare, but a number of cases have since been reported. It has been claimed that placental SSD is associated with pregnancies progressing beyond 40 weeks gestation, with less than a third of the pregnancies affected by placental SSD laboring spontaneously.[6] The majority of reported cases ended in induction of labor and/or cesarean delivery. It is thought that the rate of spontaneous labor and delivery are reduced as the enzyme deficiency is linked to an increased rate of failure to respond to endogenous or intravenous oxytocin and failure of cervical dilatation.

Generalised scaling is usually present at or shortly after birth. It is most prominent over the extremities, trunk and buttocks and usually spares the palms, soles and flexural creases. The face is usually spared with the exception of the preauricular area. STS acts on CSO4, cholesterol sulphate, a multifunctional sterol metabolite produced in the squamous keratinising epithelium. In 2004, Elias and colleagues reported that in the absence of STS, abnormal scaling occurs due to persistent cellular adhesions forming in the epidermis and reduced normal desquamation.[7] Patients with XLI therefore have a tenfold increase in CSO4 levels and 50% reduction in cholesterol levels as STS is not available to act on the CSO4. The STS gene has been mapped to the short arm of the X-chromosome (band Xp22.3).[8] The deletion of this gene is the most common molecular defect found in those diagnosed with XLI with 90% of patients showing complete deletion.[9] Usually XLI is the only clinical manifestation of

STS gene deletions, but a subset of patients will have a deletion associated with microdeletions/contiguous gene syndromes that can cause a more severe phenotype. For example, deletion of the VCX3A gene on Xp22.3 has been shown to cause XLI with an abnormal neurocognitive (intellectual disability) in some persons.[10] The frequency of contiguous gene syndromes associated with STS gene deletions is unknown. This information can be found antenatally using invasive testing (amniocentesis or chorionic villus biopsy followed by array comparative genomic hybridization (aCGH). Placental SSD is characterised antenatally by low estrogen excretion in the presence of normal fetal growth. Serum and urine estriol measurements are used for the diagnosis and management of pregnancies at risk. This is based on the fact that nearly all maternal estriol is derived from placental conversion of steroid precursors produced by the fetus. The measurement of maternal serum and urinary estriol levels therefore allows direct assessment of the function of the fetoplacental unit, especially in the third trimester.

Several clinical situations including placental SSD, primary fetal adrenal hypoplasia, anencephaly, intrauterine fetal death and severe intrauterine fetal growth restriction can present with low estriol levels in the third trimester.[11] Biochemically, affected patients have urinary estrogens that are consistently low (normal pregnancy range 40-150 μmol/24 h) and 17-oxogenic steroids are high.[12] Serum estriol levels are low (normal pregnancy range 26-28 nmol/L) while serum placental lactogen (HPL) levels are normal (4-9mU/L), suggesting normal placental function.[13]

A DHEAS loading test can be used to confirm the diagnosis of placental SSD.[14-16] However, it is an invasive test requiring the injection of 50-250 mg dehydroepiandrosterone (DHEAS) into the amniotic fluid or intravenously. Urinary estriol levels are measured over the following 24 hours. In a normal pregnancy, urinary estriol levels will rise, but in placental SSD the maternal estriol levels remain low as the placenta cannot convert DHEAS to estriol. This discriminates placental SSD from other causes of low estriol.[17]

Placental SSD presents clinically with a normal-sized fetus and may have an increased incidence of failed induction of labor or prolonged labor leading to cesarean delivery due to cervical dystocia. When low levels of unconjugated estriol (uE3) are identified, women should be counselled about the increased risk of miscarriage, fetal intrauterine growth restriction and intrauterine demise.[18] These women should have a detailed anomaly ultrasound scan and may benefit from serial third trimester growth scans. There is also a place for genetic counselling. Low uE3 levels, in combination with the other abnormal tests (AFP, βhCG) taken as part of screening tests for a chromosomal problem, is associated with a normal outcome in only 28% of cases. Low uE3 with other screening bloods negative has normal outcome at birth in 81% of cases of which the majority will turn out to have XLI/SSD (56%). Given the association of the STS gene deletions with other chromosomal microdeletions, counseling regarding outcome can be challenging. There are also rare associations between low uE3 and other conditions such as Smith-Lemli-Opitz syndrome.[19]

When placental SSD/XLI is suspected because of a previously affected baby, women may be offered genetic counselling and an early ultrasound scan from 16 weeks gestation to sex the fetus. Once a female fetus has been confirmed by ultrasound, the mother can be reassured and informed that the pregnancy is unlikely to be affected. If a male fetus is identified, further testing may be offered by checking the serum uE3 levels. If the levels of uE3 are normal then it is unlikely that the baby is affected. If the levels are low, this may point towards placental SSD and women should be offered detailed anomaly ultrasound and serial third trimester growth scans. It may also help prepare women who can be made aware of the increased risk of emergency cesarean delivery. Depending on her view of the risk of a significant gene deletion, the woman may opt to have an invasive test allowing confirmation that there are no additional microdeletions. In the United Kingdom, XLI would not be a condition that meets the level of severity where consideration for termination of pregnancy would be considered under clause E, unless there were additional problems.

Several factors have an impact on final mode of delivery as demonstrated in our two cases. There is an increased risk of failed induction of labor and cesarean delivery for women who have had a previous cesarean section. The situation is further complicated by the presence of another placental SSD-affected pregnancy. We propose that there may be a place for considering elective cesarean delivery rather than an induction of labor in these cases, but the chance of vaginal birth after cesarean cannot be excluded without the trial of labor itself. **Figure 1** illustrates our suggested management pathway of these women.

Postnatally, SSD leads to an accumulation of cholesterol sulphate in the blood, cornea and skin. This presents with ichthyosis and with corneal opacities usually at 3 to 6 months of life.[20] These opacities are found in 50% of affected males and 25% of female carriers. Cryptorchidism has been reported to affect

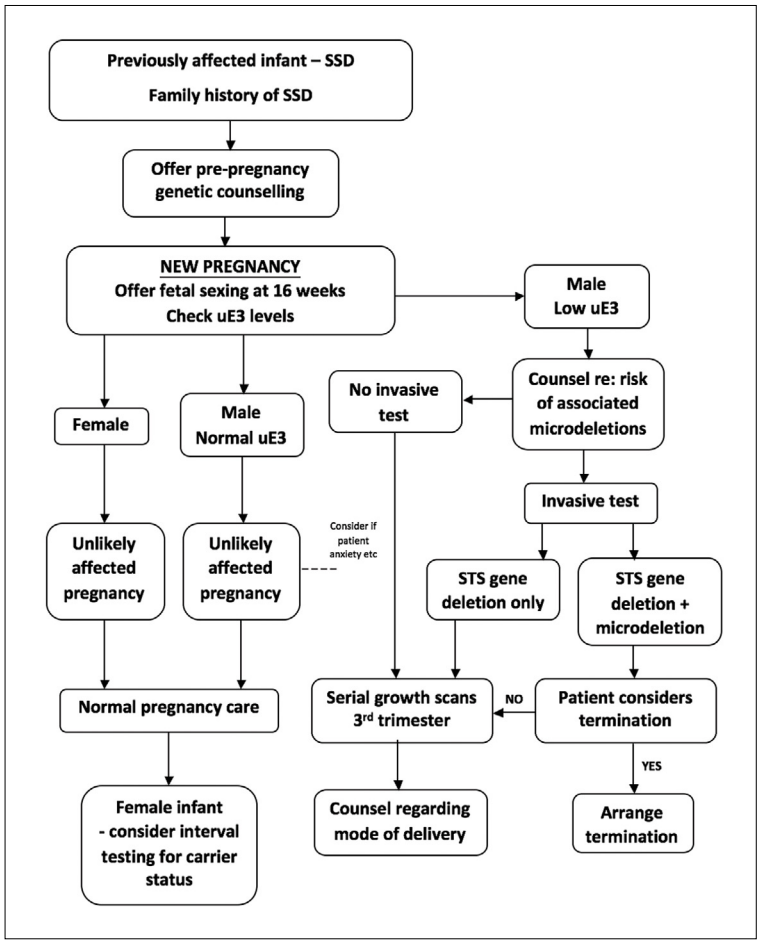

Figure 1. Suggested management pathway.

up to 20% of XLI patients, with no detrimental effects on sexual development, testosterone levels, and fertility. The most common cognitive and behavioral disorders in XLI patients include attention deficit hyperactivity disorder (ADHD, inattentive subtype), and autistic-spectrum disorder (language/communication difficulty).[21] Skin biopsies of affected infants have revealed low epidermal arylsulphatase C and almost no steroid sulphatase activity within the skin fibroblasts. It is important to note that affected males otherwise develop normally.[22] There is no definitive cure for XLI. Medical management is directed at reducing scales and decreasing skin dryness aiming to improve skin appearance.

In conclusion, congenital ichthyosis is a rare genetic disorder of keratinisation caused by steroid sulphatase (STS) deficiency, which results in a scaling skin condition in male infants shortly after birth. It may be associated with failed induction of labor and prolonged labor with a higher risk of cesarean delivery due to cervical dystocia. For women with a previously affected baby or a family history of SSD/XLI, pre-pregnancy counselling is important, and they may wish to consider prenatal diagnosis dependent on the risk of an associated microdeletion. Our pathway aims to offer affected families options to consider during future pregnancies.

Consent

Written consent obtained from both patients discussed.

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