Antenatal diagnosis of steroid sulphatase deficiency: case report and literature survey

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SUMMARY Steroid sulphatase deficiency is a recently recognised genetically determined inborn error of metabolism. Originally identified as an enzyme disorder of the placenta (commonly termed placental sulphatase deficiency), it is now known that the progeny of affected pregnancies have a generalised steroid sulphatase deficiency and that the enzyme defect persists throughout life. The disorder is characterised clinically by markedly low maternal oestrogen excretion in the presence of normal fetal growth and development. The importance of antenatal diagnosis lies in the differentiation of this disorder from the more ominous fetal defects that result in low oestrogen concentrations. This paper summarises the relevant literature and describes a case in which biochemical tests were used for the antenatal diagnosis of steroid sulphatase deficiency. The pregnancy resulted in a healthy baby boy delivered vaginally after a spontaneous labour.

The use of serum and urine oestriol measurements in the management of high-risk pregnancies is now well established. Nearly all of the oestriol present in the maternal serum or urine is derived from placental conversion of steroid precursors produced by the fetus. Therefore, maternal serum or urine oestriol concentrations reflect, primarily, the status of the fetoplacental unit. Very low third trimester oestriol levels have been associated with several clinical situations¹⁻³: (a) iatrogenic effects (antibiotics, cortisone and other drugs), (b) gross disturbances of the maternal enterohepatic circulation, (c) severe intrauterine growth retardation, (d) anencephaly, (e) fetal death, (f) primary fetal adrenal hypoplasia and (g) placental steroid sulphatase deficiency (SSD). Conditions (a) to (e) may be differentiated by the history and clinical examination. However, the latter two situations, (f) and (g) are more difficult to distinguish from one another. Fetal adrenal hypoplasia is associated with a high neonatal mortality rate as the newborn infants are likely to be at risk from adrenal insufficiency. In pregnancies with SSD there is a high incidence of difficult labour—many requiring caesarean section. Both conditions result in very low oestrogen production in the presence of apparently normal fetal growth and development. Fortunately, biochemical tests are useful in discriminating between these two conditions and the following case study illustrates their use.

Case report

A 25-year-old primigravida failed to gain weight during the 31st and 32nd weeks of pregnancy. The 24-hour urinary oestrogen output was found to be low and she was admitted for further investigation. Apart from the oestrogens, routine blood (albumin, total protein, electrolytes, urea, calcium, phosphate, liver function tests and creatinine) and urine (protein, glucose and creatinine clearance) investigations were normal. Serial urinary oestrogens over a five-day period were consistently low (average concentration 7 $\mu\text{mol}/24\text{h}$, reference range 40–150 $\mu\text{mol}/24\text{h}$). The patient continued to be clinically normal with a very active fetus and began to gain weight again. A serum oestriol at 34 wk was 10.7 nmol/l (reference range

Table 1 Concentration of steroid sulphates in maternal urine by capillary gas-liquid chromatography

Steroid sulphate ($\mu\text{mol}/24\text{h}$)	Patient	SSD (n = 10)	Normal (n = 10)
16 α -hydroxy DHA	29.99	29.57	1.76 (0.39–4.9)
16-oxo-androstenediol	5.21	5.95	0.74 (0.05–4.8)
Androst-5-ene-3 β ,16 α ,17 β -triol	17.05	18.55	1.41 (0.16–7.0)
16,18-dihydroxy DHA	1.03	6.86	0.16
Oestriol	1.76	1.14	17.25
16 α -hydroxypregnenolone	2.31	9.91	0.33 (0.06–1.38)
5-pregnene-3 β ,16 α ,20 α -triol	1.22	2.0	ND

DHA = dehydroepiandrosterone.
ND = not determined.

26–28 nmol/l) and a serum placental lactogen (HPL) concentration of 7.5 mU/l (reference range 4–9 mU/l) indicated normal placental function. Measurement of the biparietal diameter of the fetal head, using ultrasound, revealed a normal fetal growth rate. At this stage fetal adrenal hypoplasia or placental steroid sulphatase deficiency was suspected. Maternal urinary 17-oxogenic steroids were relatively high, 55 μ mol/24h (reference range 15–56 μ mol/24h) suggesting that SSD rather than fetal adrenal hypoplasia was the probable cause of the low oestrogen excretion.⁴ The patient was sent home pending confirmation of the diagnosis.

The excretion of steroid sulphates in maternal urine (Table 1) was raised when compared with normal pregnancies (gas chromatographic determination by Dr J Honour at the Clinical Research Centre, Harrow), but it was within the laboratory ranges for these compounds in 10 previous cases of confirmed SSD.⁵

Further oestriol determinations between 37 and 39 weeks were all less than 20 μ mol/24h and the pregnancy progressed normally.

At 39 wk gestation the patient was readmitted to hospital with regular contractions and ruptured membranes. She gave birth to a 3310 g boy after a four-hour labour. The infant had an Apgar score of 9 at 1 minute and appeared healthy. The post-natal course was uneventful and mother and child were discharged five days later.

The mother's previous medical history was unremarkable but her brother has a dry scaly skin condition (? ichthyosis) which the family believe to be inherited from her great-grandfather. The child's progress is being followed to see if he develops this condition.

Discussion

Placental oestrogens are produced by the metabolism of dehydroepiandrosterone sulphate (DHAS) originating from the mother and the fetus, and 16 α -hydroxydehydroepiandrosterone sulphate (16-OHDHAS), originating predominantly from the fetus. In the first step of oestriol synthesis the sulphated conjugates are hydrolysed through the action of the microsomal enzyme 3 β -yl steroid sulphatase (sterol sulphate sulphonylhydrolase, EC 3.1.6.2.). In the case of deficient activity of this enzyme the hydrolysis cannot take place and the formation of oestriol is impaired.⁶

The first case of SSD—then recognised as a placental sulphatase deficiency—was reported by France and Liggins in 1969.⁷ It was first assumed that the deficiency was extremely rare but in recent years reports have become more frequent and the literature

now contains descriptions of 66 cases.^{5,7,8,10–23,27} Apart from the low oestrogen production no other manifestations directly attributable to the sulphatase deficiency have been reported during the antenatal period nor in the infant at birth. However, some groups have observed a high incidence of pregnancies of greater than 40 wk duration.^{10,11,15,16,21} This may be a feature of the disorder related to the fact that a high percentage of patients require medical or surgical intervention to facilitate delivery.

Less than one third of the pregnancies affected by SSD ended in spontaneous labour. The majority of cases required induction of labour, caesarean section, or both. Twenty-seven cases required caesarean section,^{5,8,10,12–16,18–21,27} eleven after induction had failed,^{5,12,13,15,16,20,21,27} while in eight cases induction was successful,^{5,10,12,14} although three of these required forceps delivery because of fetal distress.^{5,15} Several cases terminated by caesarean section have been associated with an unripened cervix which failed to dilate on oxytocin administration.^{13,14,18,20} It has been postulated that the difficulties in achieving spontaneous labour and delivery may be due to the low oestrogen production.¹³ This suggests that high levels of oestrogens are necessary in preparing for and initiating labour. The low success rate of oxytocin induction and the relatively high incidence of unfavourable cervixes suggest a blunting of the normal physiological responses of pregnancy.

Many different biochemical tests have been used to aid in the antenatal diagnosis of SSD. Several groups

Table 2 Biochemical findings in fetoplacental steroid sulphatase deficiency

Sample	Substance	Finding	References
Maternal urine	17-oxogenic steroids	High	4
		normal	
Maternal plasma	17-oxosteroids	Raised	19
	Pregnanediol	Normal	13, 14, 19, 21
	Pregnanetriol	Normal	12
	Progesterone	Normal	18
	Progesterone	Low	14, 19
	17 β -oestradiol	Low	14
	17-hydroxyprogesterone	Low	14
	17 β -hydroxycorticosteroid	Low	14
	Corticosteroid binding globulin	Low	14
	HPL	Normal	8, 16, 17
Amniotic fluid	HCG	Normal	16, 17
	Cortisol	Normal	19
	Pregnanetriol	Raised	14
	DHAS	Raised	16, 17
	DHA	Normal	16, 17
	Androstenedione	Normal	16, 17
	Testosterone	Normal	16, 17
Cord blood	16-hydroxy DHAS	Normal	13, 15, 16
	DHAS	Normal	13, 15, 16

HPL = human placental lactogen.

DHA = dehydroepiandrosterone.

HCG = human chorionic gonadotrophin.

DHAS = dehydroepiandrosterone sulphate.

have investigated maternal urine and plasma steroid content while others used amniotic fluid. The findings of these workers are summarised in Table 2. The most commonly used test for the diagnosis of SSD is a "dynamic" procedure—the DHAS loading test.^{7 10 11 13 15 16 21 27} For this test a solution containing DHAS (50–250 mg) is injected into the amniotic fluid or intravenously and the excretion of oestriol determined during the following 24-hour period. In a normal pregnancy the maternal urinary oestriol concentration rises by between 10 and 30 $\mu\text{mol}/24\text{h}$ depending on the amount of DHAS administered, as it is metabolised and removed through the maternal circulation. Measurement of plasma oestradiol 1 h and 3 h after infusion is equally suitable.¹⁶ In SSD pregnancies the placenta cannot convert DHAS to oestriol so the maternal urinary oestriol remains very low. The diagnostic significance of the test can be enhanced by administering a DHA load in the same way. As the metabolism of DHA to oestriol can proceed in the absence of the sulphatase enzyme the maternal oestrogen output should rise in both normal and SSD cases.^{7 13} Although this is a useful way of detecting SSD *in vivo* it has the major disadvantage of being invasive particularly when the DHAS is injected into the amniotic sac with consequent risk to the fetus.

To differentiate between SSD and fetal adrenal hypoplasia Oakey⁴ measured maternal urinary oestrogens and 17-oxogenic steroids during the third trimester. He concluded that oestrogen excretion less than 11.5 $\mu\text{mol}/24\text{h}$ and 17-oxogenic steroids greater than 26 $\mu\text{mol}/24\text{h}$ were characteristic of pregnancies with SSD.

Recently Taylor and Shackleton⁵ have applied capillary gas chromatography to the assay of steroid monosulphate fractions of maternal and neonatal urine. They have demonstrated a characteristic profile of steroid sulphates in maternal urine which is diagnostic of SSD (Table 1). A similar method has been used by Phillipou *et al.*²³ These methods would appear to be the best way of diagnosing SSD antenatally and are likely to gain more widespread use in the coming years as obstetricians and clinical chemists become more aware of this deficiency. Before these methods were available *in vitro* studies of the placenta's ability to hydrolyse isotopically labelled sulphated oestriol precursors were recommended for definitive proof of SSD. In the SSD cases reported so far the sulphatase activity has seldom been greater than 4% of the control placenta and is often undetectable.

Preliminary findings by McNaught and France²⁵ suggest that the biochemical basis of SSD may be a defect in membrane-enzyme structure which prevents the normal function of the enzyme.

With the notable exception of two pregnancies with apparently low placental steroid sulphatase activity⁸ all the confirmed cases of SSD have resulted in male infants. In 1977 Shapiro *et al.*²⁰ reported the association of SSD and X-linked ichthyosis. They demonstrated the absence of steroid sulphatase enzymes in cultured fibroblasts from a patient born of a pregnancy affected by placental SSD. This work has been confirmed both in a later study of five cases by Shapiro *et al.*⁹ and by the work of Jöbsis *et al.*^{10 21} on six cases in Holland. The skin of affected infants usually remains normal for the first 3–6 months of life, after which ichthyosis becomes recognisable and persists throughout the life of the individual. The ichthyosis itself appears to be caused by the deficiency of the enzyme arylsulphatase C in the epidermis, although its role in the process of keratinisation is still unknown. Ichthyosis has now been reported in association with one-fifth of the cases of SSD. This association with a known X-linked disorder and the very high male:female ratio strongly suggests that SSD is an X-linked disorder, although autosomal dominant transmission with sex-linked expression cannot be totally excluded.⁶

Many cases of SSD probably go undetected since affected pregnancies follow a normal antenatal course. It has been estimated that as many as one 3000 pregnancies is affected.²⁶ Routine screening all third trimester pregnancies for oestriol excretion would probably reveal many more cases of SSD and perhaps other associated defects of steroid metabolism.

The finding of a consistently low maternal urinary or plasma oestriol in company with apparently normal fetal development should alert the chemical pathologist/biochemist to the possibility of SSD and the need for confirmatory tests.

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