PAPERS AND ORIGINALS

Incidence of anencephaly and other major malformations when oestriol excretion is very low

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Summary

A study of 533 women with very low urinary oestriol excretion during the third trimester of pregnancy showed an incidence of major fetal malformations among their infants of 7.1%, and a perinatal mortality rate of 14.6%. Thirteen of the malformations were cases of anencephaly, and 26 of the 78 perinatal deaths were due to or associated with major fetal malformations. The incidence of these complications was higher when maternal oestriol excretion was lower. Routine screening by urinary oestriol assay, with fetal radiography when values below 20.8 $\mu\text{mol}/24$ hours (6 mg/24 h) are detected, is the most reliable method of detecting anencephaly before birth.

Introduction

To improve the standards of antenatal care and reduce perinatal mortality and morbidity routine testing of placental function during the last trimester of pregnancy has often been advocated.¹⁻³ Measuring urinary excretion of oestriol is the most widely used test of fetoplacental function, for it is well known that subnormal oestriol excretion is associated with higher incidences of perinatal mortality, intrauterine growth retardation, and major fetal malformations.⁴

Frandsen and Stakemann noted the classical association that exists, because of fetal adrenal hypoplasia, between anencephaly and very low levels of maternal urinary oestriol excretion.⁵ Nevertheless, the likelihood of anencephaly being present when

subnormal oestriol excretion is detected has not been established. This information is important, because caesarean section might be performed in the mistaken belief that the low level of oestriol was due to fetal hypoxia. We routinely measure oestriol excretion in all our patients and were able to calculate the incidence of anencephaly and other anomalies according to the degree of impairment of oestriol excretion. We present here our findings.

Patients and methods

From February 1971 to August 1976 routine urinary oestriol excretion assays were performed on 12 484 consecutive patients who were delivered at the Mercy Maternity Hospital, Melbourne. Oestriol assays were initially performed at 30 to 32 weeks of gestation and repeated when there were complications such as hypertension and pre-eclampsia or when low oestriol excretion was detected.

Urinary oestriol excretion was measured by the rapid method of Brown *et al.*⁷ The lower limit of normal was defined as a line joining 27.8 $\mu\text{mol}/24$ hours (8 mg/24 h) at 30 weeks' gestation and 41.6 $\mu\text{mol}/24$ hours (12 mg/24 h) at 40 weeks and thereafter.⁸ This line corresponds roughly to the tenth centile for a normal obstetric population.

The present series of patients consisted of all women whose urinary oestriol excretion was 20.8 $\mu\text{mol}/24$ hours (6 mg/24 h) or less on one or more occasion when assayed during the last trimester of pregnancy.

Results

Urinary oestriol excretion was subnormal in 1640 of the 12 484 patients tested (13.1%). In 533 of these patients (4.3%) oestriol excretion was 28.8 $\mu\text{mol}/24$ hours or less on one or more occasion. Fourteen of the infants born to the 12 484 mothers had anencephaly, and in all except one case the mother's urinary oestriol excretion had been below 6 mg/24 hours. One woman whose lowest oestriol value had been 13 mg/24 h delivered twins, one of whom was anencephalic.

Table I shows the incidence of anencephaly and other major fetal malformations according to the level of oestriol excretion. The total incidence of major fetal malformations was 7.1% (13 cases with anencephaly and 25 with other malformations). The incidence of these complications increased as maternal oestriol excretion became lower.

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TABLE I—Incidence of anencephaly and other major fetal malformations according to maternal urinary oestriol excretion

Urinary oestriol excretion		No of patients	No (%) of infants with anencephaly	No (%) with other major malformations
mg/24 h	μmol/24 h			
≤1.0	≤3.5	27	2 (7.4)	1 (3.7)
2.0	6.9	47	4 (8.5)	5 (10.6)
3.0	10.4	76	4 (5.3)	2 (2.6)
4.0	13.9	93	1 (1.1)	5 (5.4)
5.0	17.4	128	2 (1.6)	10 (7.8)
6.0	20.8	162	0	2 (1.2)
Total		533	13 (2.4)	25 (4.7)

Table II shows the incidence of stillbirths and neonatal deaths according to the level of maternal oestriol excretion. The total perinatal mortality rate, 14.6%, confirmed the high-risk nature of the pregnancies studied. The perinatal mortality rate increased with lower maternal oestriol levels. Of the 78 perinatal deaths 13 were due to anencephaly (eight stillbirths and five neonatal deaths) and a further 13 were due to or associated with other major fetal malformations. In 21 of these 26 deaths (80.8%) the malformation was detectable on a plain radiograph of the pregnant abdomen (table III). The five neonatal deaths associated with major fetal malformations not detectable by antenatal radiography included two cases with ventricular septal defect, one with anomalous pulmonary venous drainage, one with exomphalos, and one with hypospadias. One fetus with microcephaly did not die. Twenty-two of the 38 major fetal malformations (57.9%) were therefore diagnosed by antenatal radiography.

TABLE II—Incidence of stillbirths and neonatal deaths according to maternal urinary oestriol excretion

Urinary oestriol excretion		No of patients	No (%) of stillbirths	No (%) of neonatal deaths	No of perinatal deaths due to or associated with major fetal malformations
mg/24 h	μmol/24 h				
≤1.0	≤3.5	27	7 (25.9)	2 (7.4)	3
2.0	6.9	47	11 (23.4)	5 (10.6)	7
3.0	10.4	76	11 (14.5)	7 (9.2)	5
4.0	13.9	93	7 (7.5)	6 (6.5)	2
5.0	17.4	128	8 (6.3)	4 (3.1)	7
6.0	20.8	162	8 (4.9)	2 (1.2)	2
Total		533	52 (9.8)	26 (4.9)	26

TABLE III—Radiologically detectable malformations

Malformation	No with malformations	No who died
Anencephaly	13	13
Iniencephaly	2	2
Hydrocephaly	2	2
Microcephaly	1	—
Sacral teratoma	1	1
Hydrops fetalis	2	2
Multiple, including skeletal	1	1
Total	22	21

Discussion

Our findings show that the risk of perinatal death and major malformations dramatically increased when maternal oestriol excretion was below 20.8 μmol/24 hours. Patients with these low levels constituted 4.3% of the antenatal population, and they presented a challenge of diagnosis and appropriate management to improve mortality and morbidity statistics. On rare occasions very low levels of oestriol excretion may be associated with placental sulphatase deficiency or primary fetal adrenal hypoplasia,⁹ in which case there is no risk to the fetus in utero, although the newborn infant with adrenal hypoplasia requires early steroid treatment.

The incidence of major fetal malformations is approximately doubled when pregnancy is complicated by subnormal oestriol excretion.¹⁰ This observation has led some workers to believe that caesarean section should not be undertaken for purely fetal reasons if maternal oestriol excretion is subnormal, lest the fetus is malformed.¹¹ We have shown that plain radiography of the maternal abdomen when oestriol excretion is very low will identify about 80% of cases of fetal malformation that may cause or be associated with fetal death. If the radiograph is normal conservative treatment of intrauterine growth retardation,^{12 13} or delivery if the fetus is mature enough, should be considered.

In our study all but one case of anencephaly was associated with oestriol excretion of 20.8 μmol/24 hours or less, the exception occurring when there was a normal accompanying twin. In all 12 cases reported by Macafee *et al*¹⁰ the maternal oestriol excretion was 20.8 μmol/24 hours or less. Sixteen of the 17 cases reported by Frandsen and Stakemann⁶ were associated with oestriol values of 16.3 μmol/24 hours (4.7 mg/24 h) or less; in the remaining case the mean oestriol value was 34 μmol/24 hours (9.8 mg/24 h) and the fetal adrenals were of normal size. Therefore in the combined evaluation of these series 41 of the 43 cases of anencephaly would have been diagnosed on the basis of very low oestriol excretion.

Early diagnosis of anencephaly is desirable so that later obstetric problems, including polyhydramnios, antepartum haemorrhage, and shoulder dystocia may be prevented. Anencephaly can be diagnosed early in the second trimester by ultrasound scanning and detection of raised amniotic fluid α-feto-protein levels. These tests are impractical for general use so only selected patients are tested: women who have had an anencephalic infant, women with diabetes mellitus, and those with a family history of central nervous system malformations. Nevertheless, investigation of these patients will detect only about 10% of the total affected pregnancies.¹⁴ The presence of anencephaly may be suspected in late pregnancy, when there is polyhydramnios or the fetal head cannot be palpated, but up to 70% of cases may remain undiagnosed until the onset of labour or after birth.¹⁴ Our findings indicate that the most reliable means of detecting anencephaly is by fetal radiography when routine urinary oestriol values have been found to be very low.

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