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High oestrogen excretion in pregnancy

I. R. McFADYEN *Consultant Obstetrician and Gynaecologist*, H. G. J. WORTH* *Principal Biochemist*, D. J. WRIGHT *Senior Biochemist* & S. S. NOTTA† *Registrar, Divisions of Perinatal Medicine and Clinical Chemistry, and Department of Obstetrics and Gynaecology, Northwick Park Hospital, and Clinical Research Centre, Watford Road, Harrow, Middlesex HA1 3UJ, UK*

Summary. Fifty-one women with singleton pregnancies whose urinary oestrogen excretion was above the 95th centile of the hospital's reference range on two or more occasions were reviewed. The women did not differ from the general population in race, parity, age, height or weight gain during pregnancy, but they were slightly heavier. Fetal and placental weights were greater than the corresponding values in the general population, as were the volumes of urine containing the oestrogen, but none of these differences was sufficient to account for oestrogen excretion above the 95th centile. Eleven patients has a glucose tolerance test, two of them had abnormal results and nine had normal results but heavy babies. Patterns of oestrogen excretion did not identify a high-risk population but the women with consistently high excretion gave birth to eight of the nine babies that weighed $\geqslant$4 kg in this population. Twenty-two of the women had 23 subsequent pregnancies in which oestrogen excretion was measured: excretion was normal in 17, low in two and above the 95th centile in four.

High oestrogen excretion in pregnancy might reflect fetal stress. Some obstetricians consider that it does, but while there is a copious literature on the clinical significance of low oestrogen excretion we can find only one paper on high levels of oestrogen in the urine in pregnancy (Beischer *et al.* 1968) and the topic is not mentioned in recent reviews. Beischer *et al.* (1968) found that oestriol excretion above the 90th centile provided assurance that the fetus was not in jeopardy. Since this is contrary to some clinicians' experience, we examined the pregnancies and their outcome in 51 women whose urinary oestrogen excretion was above the 95th centile.

Patients and methods

Urinary total oestrogen determination was carried out by a modification of the automated fluorometric method of Hainsworth & Hall (1971). A reference range for this method was previously produced by collating results of 16 700 estimations (McFadyen *et al.* 1980). Patients who had during a pregnancy two or more 24 h specimens of urine that contained total oestrogens above the 95th centile of this reference range were extracted from all who had estimations carried out over 4 years. A total of 137 patients fulfilled this criterion; the notes and data of the first 51 of these with singleton pregnancies were reviewed. Fetal anomaly was not an exclusion criterion but there were no major anomalies among the 51.

The majority of requests for oestrogen estima-

*Present address: Department of Clinical Chemistry, Kings Mill Hospital, Sutton-in-Ashfield, Nottinghamshire NG17 4JL, UK.
†Present address: Rashid Hospital, Dubai, United Arab Emirates.

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tion in these patients were made for clinical reasons, but some were made as part of other prospective research programmes. The urine was collected from both in- and out-patients after they had been instructed in the accurate collection of 24-h specimens of urine, reinforced by printed instructions. An estimated date of delivery was obtained for each patient by calculation from the first day of the last menstrual period if this was known, by clinical assessment of uterine size and by ultrasonic measurement of fetal size before 20 weeks if this was necessary. The specimens were obtained at various times between 28 weeks and delivery.

Birthweights are expressed both in kilograms and in standard deviations (SD). The latter are derived from the birthweight corrected for gestational age, maternal size and parity and fetal sex by using the nomogram of Altman & Coles (1980) constructed from the data of Thomson *et al.* (1968).

Results

A total of 366 24-h collections of urine were obtained from the 51 patients (mean 7·18 per patient) of which 186 (51%) contained oestrogens above the 95th centile of the reference range (mean 3·65 estimations per patient). Most of the collections were obtained after the 35th week of pregnancy so the majority of the results above the 95th centile were obtained late in pregnancy, but one was as early as 29 weeks.

The mean urinary volume in the specimens with high oestrogen content was 1·75 (SD 0·52) litres. The mean volume in 10 000 consecutive specimens from the reference range was 1·42 (SD 0·53) litres. This difference is statistically significant but the greater volume with the high levels is not sufficient to account for the oestrogen excretion being above the 95th centile.

The racial mixture of the 51 women reviewed here reflected that of all women delivered in the hospital over that period: 44 were European, two Negroid and five Indian. Eighteen were nulliparous and 33 parous; only 13 smoked. Their ages were between 18 and 41 years (mean 28·2 years) and their height was between 156 and 177 cm (mean 164 cm). Forty-seven women were weighed at 18/22 weeks (or an approximate weight for that gestational age was calculated from their known weights at 12–16 weeks and at 28 weeks), the range of these weights was from 52 to 96 kg (mean 68·2 kg). The remaining four patients did not attend the clinic at either 20 or 28 weeks and so a mid-pregnancy weight was not available: they were, however, weighed at 30–32 weeks and were then between 66 and 77 kg (mean 71·25 kg). Weight gain from 27–32 weeks to delivery was between −0·25 and +0·85 kg/week (mean 0·32 kg/week) and in the final 4 weeks of their pregnancies between −0·15 and +0·85 kg/week (mean +0·25 kg/week). The maximum systolic blood pressures recorded for these patients were between 108 and 164 mmHg (mean 136 mmHg) and the diastolic between 63 and 107 mmHg (mean 85 mmHg).

Glucose tolerance tests were carried out on 11 patients: two of these were abnormal. The indication for both of the tests which had abnormal results was a family history of diabetes; both patients were dieted for the remainder of the pregnancy; their babies weighed −0·5 and +0·8 SD from the mean for their gestational age. The indications for glucose tolerance tests in the other nine patients were a family history of diabetes in four, a bad obstetric history in two, persistent glycosuria in one and previous babies weighing >4 kg in two. These last two patients were delivered of babies with SD scores of +1·6 and +2·9; the other seven had babies whose SD scores ranged from −0·4 to +3·3 (mean +1·48) (Table 1).

The maturity of the 51 pregnancies at delivery was between 37 and 41 completed weeks (mean 39·4 weeks). Labour which ended with vaginal delivery started spontaneously in 25 patients and was induced in 18. Elective caesarean section was carried out in three and during labour in five (three spontaneous onset and two induced). A possible relation between the level of oestrogen excretion and the time of onset of labour could not be reviewed as not all of the women had as

Table 1. Standard deviation scores of birthweight in 11 patients who had oral glucose tolerance tests

Glucose tolerance	Oestrogen excretion pattern		
	I	II	III
Abnormal	—	—	+0·8 −0·5
Normal	+0·8 +1·3 +1·6	+2·3	+1·15 +3·3 +2·9 −0.4 +1·1

estimation within a few days of delivery. The length of labour was, however, reviewed as it appeared to be short (Fig. 1); the first stage only was considered as the second stage might be dependent on different policies of intervention. In nulliparae the first stage of spontaneous labour (mean 8·69 h) was significantly longer than that of induced labour (mean 7·32 h) (P <0·001) (Table 2); similarly, in parous women the length of induced labour was significantly shorter than that of spontaneous labour (P <0·001). When these induced labours were compared with 694 induced labours during 1 year at the hospital (286 primigravidae and 408 multiparae) no statistically significant differences were found in the length of the first stage.

All 51 infants were live born and there were no neonatal deaths; 28 were female and 23 male with birthweights ranging from 2·61 to 4·98 kg (mean 3·6 kg). The SD scores of birthweight corrected for gestational age, maternal size and parity and fetal sex were between −1·6 and +3·6 (mean +0·64). Fetal distress developed during labour in 11 patients and two newborn babies had Apgar scores of 5 without precedent signs. Fetal distress was shown in six patients by late decelerations of the fetal heart, in four by abnormalities of the fetal heart rate accompanied by meconium staining and in one by meconium staining with an Apgar score of 4 at delivery.

The placentas weighed between 500 and 1100 g (mean 702 g). They weighed between one quarter and one seventh of the weight of their fetuses, with the exception of a 1100 g placenta which had co-existed with a 3·46 kg normal fetus. The range of combined weights of placenta and fetus was between 3·21 and 5·98 kg (mean 4·32 kg).

Table 2. Length of the first stage of labour in 43 women who had vaginal deliveries

Labour	*n*	Length of first stage (h) Mean	Range
Spontaneous			
Nulliparous	10	8·69	3–16·5
Multiparous	15	4·39	1·33– 9·5
Total	25	6·11	1·33–22·5
Pattern I	7	5·98	1·33–14·5
Pattern II	3	4·25	2·5 –16·5
Pattern III	15	4·32	1·5 –16·5
Induced			
Nulliparous	7	7·32	2·5 –27·5
Multiparous	11	4·01	1·5 – 7·5
Total	18	5·2	1·5 –27·5
Pattern I	4	9·5	1·5 –27·5
Pattern II	3	5·43	3·5 – 7·5
Pattern III	11	3·7	2·0 – 6·5

Oestrogen excretion was again measured at this hospital in 23 subsequent singleton pregnancies in 22 of these women. Oestrogen excretion was in the normal range in 17, below the 5th centile in two (an anencephalic fetus and a stillbirth), and above the 95th centile in four, one of which was complicated by hypertension but the other three were normal.

Patterns of oestrogen excretion

Maternal urinary oestrogen excretion fell into three recognizable patterns: I. Continuous steep rise (Fig. 2): 11 patients; II. Rising to a peak and then plateauing or falling (Fig. 3): 7 patients; III. Fluctuating variable pattern rising roughly

Fig. 1. Length of the first stage of labour in patients who had vaginal deliveries. ▩, Spontaneous; □, induced.

parallel to the mean of the reference range (Fig. 4): 33 patients.

These three patterns were reviewed individually to assess whether one or all were of any particular consequence. There were no significant differences between the groups in maternal size, weight gain during pregnancy or smoking habits (Table 3). Clinically significant chronic

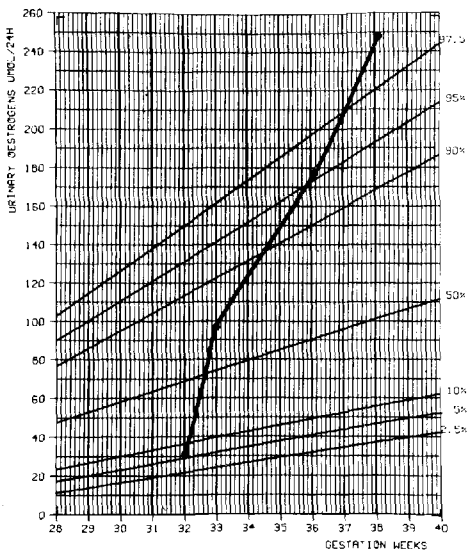

Fig. 2. An example of the pattern of oestrogen excretion in those patients in which there was a continuous steep rise.

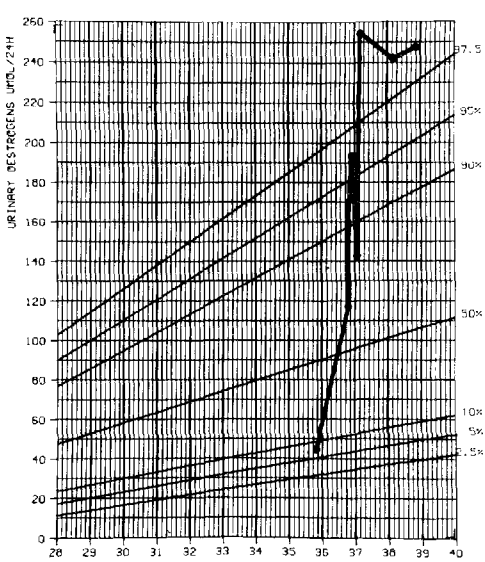

Fig. 3. Oestrogen excretion in a patient which rose steeply and then plateaued.

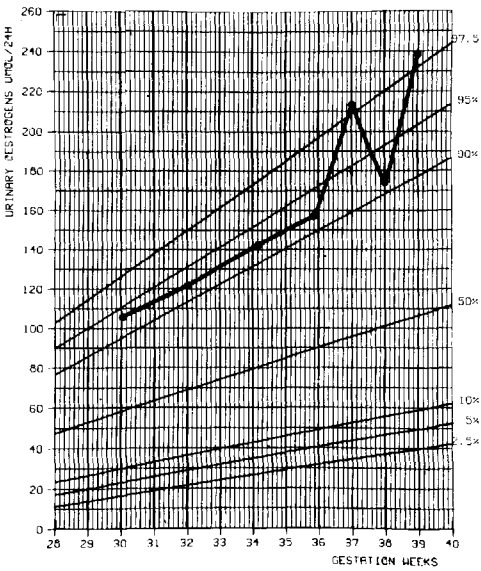

Fig. 4. High oestrogen excretion rising roughly parallel to the mean of the reference range.

abnormalities occurred in 25 of the pregnancies: persistent hypertension of $\geqslant$140/90 mmHg (19), weight loss for $\geqslant$3 weeks before delivery (4) and antepartum haemorrhages from normally situated placentas (2). Eight (73%) of those with oestrogen excretion pattern I had such an abnormal pregnancy, three (43%) of those with pattern II and 14 (42%) of those with pattern III.

Fetal distress appeared during labour in 13 (27% of those who laboured); this was shown by late or variable decelerations in seven, the passage of fresh meconium in three and an Apgar score of 4 or 5 in three. Of the 13 patients with fetal distress, five had oestrogen excretion pattern I (56% of those who laboured), one had pattern II (17%) and seven had pattern III (21%). Although birthweight, placental weight and total weight of the conceptus were not significantly different in the three groups eight of the nine babies with a birthweight of $\geqslant$4 kg and three of the five placentas that weighed $\geqslant$1 kg were in the group with pattern III. Glucose tolerance tests were most often indicated in women with oestrogen excretion pattern III and both of the abnormal results were in this group (Table 1); the two women with abnormal results were dieted and their babies had birthweights of +0·8 and −0·5 SD, while those with normal results had a mean birthweight of +1·67 SD.

Discussion

Large fetuses or placentas did not explain the

Table 3. Maternal and fetal characteristics of the 51 pregnancies according to the patterns of oestrogen excretion

Characteristic	Pattern I (n=11)	II (n=7)	III (n=33)
Maternal			
Mean height (cm)	165	165	163·5
Mean weight at 20 weeks (kg)	66·91	68·71	74·73
Weekly weight gain 28 weeks to delivery (kg)	0·40	0·32	0·32
Final 4 weeks (kg)	0·21	0·40	0·22
Smokers (n)	2	4	7
Complications (n)	8	3	14
Glucose tolerance tests			
Normal (n)	3	1	5
Abnormal (n)	—	—	2
Oestrogens in other pregnancies			
High (n)	1	—	4
Normal (n)	5	2	8
Low (n)	—	—	2
Fetal			
Mean birthweight (kg)	3·5	3·63	3·58
Mean SD score	+0·48	+0·61	+0·58
Signs of fetal distress (n)	5	1	7
Mean placental weight (g)	680	772	694
Mean weight of fetus and placenta (kg)	4·23	4·41	4·32

high oestrogen excretion in these 51 mothers. Although some were heavy, particularly in the women with consistently high excretion, the mean fetal and placental weights were not high. This is in accord with other relations of birthweight to oestrogen excretion since, although there is a direct relation with birthweight when it is low (Loriaux *et al.* 1972), this does not hold for birthweights >2·5 kg (Klopper & Billewicz 1963). Another possible fetal explanation is adrenal hyperplasia in response to stress. Oestriol excretion does correlate with fetal adrenal weight (Frandsen 1963) and normal fetal adrenals can compensate sufficiently for absence of maternal adrenals to produce oestrogens in the normal range (Charles *et al.* 1971). Hyperplastic adrenals are present in some fetuses with severe Rhesus isoimmunization (Potter & Craig 1976) and high oestriol excretion is often associated with this condition even when fetus and placenta are not heavy (Klopper & Stephenson 1966). A direct association with oestrogen excretion above the 95th centile has been shown in one fetus with adrenocortical hyperplasia (Cathro *et al.* 1969). Other observations which support a fetal contribution to high oestrogens is the pattern of excretion in the 15 women in the present series in whom oestrogens were measured from 28 to 33 weeks until close to term. While in five of these the oestrogens were above the 80th centile at the first measurement and remained there (Fig. 4), 10 started between the 10th and 75th centiles and rose to the 95th centile at 33–35 weeks (Fig. 2) which is when the fetal contribution begins to rise above the maternal (Klopper & Billewicz 1963).

Most of the estimations were requested because of possible fetal stress. That only 13 of the 51 fetuses actually developed signs of distress is not very convincing corroboration of actual fetal stress. Although fetal heart-rate abnormalities or other signs did appear in 46% of those with rapidly rising oestrogens, they did so in only 14% of those in whom oestrogen excretion plateaued or fell. It is the latter group who would be expected to be failing to compensate for stress. Possibly the explanation is that in none did the fall approach the 35% which signifies fetal hazard in diabetes (Goebelsmann *et al.* 1973) or exceed the normal 20% day-to-day variation (Klopper *et al.* 1969). These limits of variability were established for oestriol, but all classical oestrogens show day-to-day variability (Russell 1959) and since oestriol is the principal oestrogen in late pregnancy these proportions are probably true for total oestrogens. Thus it is possible that a plateau is reached when the feto-maternal unit has successully adapted to stress.

The duration of the first stage of labour was examined in detail since the initial impression from analysis of the data was of short labours, which would have shown the opposite trend of long labours found in patients with low oestrogens due to placental sulphatase deficiency (Taylor & Shackleton 1979). Although 10 patients had a first stage lasting ⩽3 h, the range of the remaining labours was wide and statistical analysis showed no differences from the general hospital population.

There is a considerable maternal component to oestrogen excretion in the last trimester (Harkness *et al.* 1966; Siiteri & MacDonald

1966). That 11 of 51 mothers in the present series required glucose tolerance tests might suggest an underlying metabolic difference which would account for the high oestrogen excretion. Certainly oestrogen excretion frequently is high in diabetic pregnancies (Goebelsmann *et al.* 1973): in one series 25% of oestrogens were above the 95th centile (Scommegna & Chattoraj 1967). There were, however, no other suggestive maternal characteristics; the women were not tall and their weight gain during the pregnancy was in the normal range and, although they were slightly heavier than the general population (Thomson *et al.* 1968), this was not sufficient to account for oestrogen excretion above the 95th centile. A maternal predisposition to high oestrogen excretion appears to be unlikely when the 22 patients who had oestrogens measured in other pregnancies are reviewed; only four were again above the 95th centile and the lone patient who had measurements in two subsequent pregnancies had high levels in one but normal in the other.

Review of these 51 pregnancies with very high oestrogen excretion has revealed no consistent pattern of fetal or maternal characteristics. While a continuing rapid rise of oestrogens may sometimes indicate an increased risk of fetal distress, and a consistently high level a large conceptus, the overall significance of high oestrogen excretion might be that the mother and fetus are responding adequately to stress.

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