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THE CLINICAL VALUE OF OESTRONE–OESTRADIOL ESTIMATION COMPARED WITH THAT OF OESTRIOL ESTIMATION IN PATHOLOGICAL PREGNANCIES

P. I. JØRGENSEN and V. AASTED FRANDSEN

Department of Obstetrics and Gynaecology (Professor Dyre Trolle and Børge Sørensen, M.D.), University Hospital of Copenhagen, Rigshospitalet, and the Hormone Department (Chr. Hamburger, M.D.), Statens Seruminstitut, Copenhagen, Denmark

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SUMMARY

The main purpose of the present study has been to judge the clinical significance of oestrone + oestradiol estimation compared with that of oestriol estimation and the clinical value of the oestriol/oestrone + oestradiol ratio in pathological pregnancies.

For that purpose the excretions of oestrone + oestradiol and oestriol were investigated in 52 patients with complicated pregnancies. A total of 229 estimations were done.

The principal findings were:

(1) The oestrone + oestradiol assay can be useful to the clinician in the assessment of the foeto-placental function.

(2) However, the clinical significance of the oestriol estimations appeared to be better, especially concerning the diagnosis of retarded foetal growth.

(3) The oestrone + oestradiol estimations did not provide any essential information not obtainable by means of the oestriol assay.

(4) The oestriol/oestrone + oestradiol ratio appeared to be of no use to the clinician.

Thus from a clinical point of view no further advantage can be derived from the oestrone + oestradiol estimation compared with the oestriol assay and neither does a combined use of the two methods appear to be profitable.

DURING RECENT years the urinary oestrogen excretion in late pregnancy has been of increasing value to the clinician.

For many reasons interest has been focused on one compound: oestriol. It is excreted in very large quantities during pregnancy, and consequently the oestriol assay is relatively simple, rapid and not expensive compared with the estimation of other oestrogen metabolites. Furthermore an extensive literature indicates a good correlation between the oestriol output and the condition of the foetus [1, 2].

However, in some cases oestriol excretion fails to give sufficient information, or the clinician is in doubt as to how to judge the oestriol values. For that reason further investigations are required to elucidate whether abnormalities in the foetal development or other pathological conditions during pregnancy alter the excretion of other oestrogenic compounds derived from the foeto-placental unit, hoping that these will afford information in the cases where oestriol estimations are valueless, e.g. rhesusimmunization.

Much work has been done to detect new oestrogen metabolites from pregnancy urine, and at present some 20 oestrogens have been isolated [3]. However, for methodological, economic and other reasons it is a long way from the hormone laboratory to the clinic. Thus so far only the other two "classical" oestrogens,

oestrone and oestradiol, appear to fulfil the conditions necessary for hormone assay in clinical practice:

(1) An acceptable theoretical background.
(2) An analytical method applicable to the clinic.
(3) A sufficient knowledge of the excretion limits in normal pregnancy.

From a theoretical point of view there are reasons to focus attention on oestrone and oestradiol. In all probability the precursors of these two hormones as well as those of oestriol are aromatized in the placenta, but many investigations indicate that the metabolic pathways are different. Experiments with labelled material and involving foetal perfusion [3] suggest that oestrone and oestradiol are produced by the so called 'phenolic' pathway (i.e. dehydroepiandrosterone → androstenedione → oestrone → oestradiol). Probably a great deal of oestrone is secreted by the placenta to the fetal compartment and 16-hydroxylated in the fetal liver to oestriol. However, the quantitatively most important pathway for the production of oestriol is certainly the 'neutral' one, i.e. 16-hydroxylation of dehydroepiandrosterone in the fetal liver followed by aromatization in the placenta. Thus the evidence points to the fact that the excretion of oestrone + oestradiol reflects one and the oestriol output another metabolic function of the placenta, and consequently estimations of oestrone and oestradiol might be useful in cases where the oestriol values alone leave the clinicians in doubt.

Few reports are available concerning the excretion of oestrone and oestradiol in pathological pregnancies. On the basis of a relatively small number of patients the excretion of oestrone, oestradiol and oestriol has been investigated in pregnancies complicated with toxemia [4], uteroplacental insufficiency [5], diabetes [6] and other disorders [7]. It was found that in all patients with intrauterine fetal death and in most other severe cases the excretion of all three oestrogens was low or decreasing. However, in some cases of severe toxemia [4] and diabetes [6] the excretion of oestrone and oestradiol was normal in contrast to a low oestriol output. Würterle [4] suggested that 'placental insufficiency' affects the production of oestriol previous to that of oestrone and oestradiol.

The ratio oestriol/oestrone + oestradiol has been the object of some attention [6, 8, 9]. The calculated values of normal pregnancies show pronounced variations and for that reason there has been doubt as to the clinical usefulness of this ratio. The above-mentioned theoretical reflections could be a reason for further investigations in this field.

A simple and clinically useful routine method for the simultaneous estimation of oestrone and oestradiol in human pregnancy urine has been described by Frandsen [10] (see "Methods"). According to this method and based on 242 24 h urine samples from 16 women Frandsen and Lundwall [8] calculated the mean values, extreme values and 95% confidence limits for the excretion of oestrone and oestradiol in normal pregnancy. They found the output to increase during pregnancy, rising from about 200 μg/24 h in the 13th week to about 2000 μg/24 h around term. These values agree with those reported by most other investigators.

The main purpose of the present study has been to judge the clinical significance of the excretion of oestrone–oestradiol and the oestriol/oestrone + oestradiol ratio in pathological pregnancies.

METHODS

Oestrone and oestradiol were estimated together according to the method of Frandsen [10] and oestriol according to the method of Frandsen [11].

MATERIAL

The clinical material consisted of 52 patients admitted to the University Department of Obstetrics and Gynaecology, Rigshospitalet, Denmark, during the years 1966–68.

A total of 229 24 h urine specimens were analysed with reference to oestrone + oestradiol and oestriol, and the oestriol/oestrone + oestradiol ratios were calculated.

In all cases manifest or suspected abnormal clinical conditions justified the estimations.

The material was divided into five groups according to the type of excretion. The patients of groups 1, 2 and 3 had identical normal, low and normal-low excretion of oestrone + oestradiol and oestriol respectively. In groups 4 and 5 the type of excretion was different (Table 1).

These five groups were analysed with reference to the complications of pregnancy justifying the estimations (Table 2), the type of delivery (Table 3) and in particular the condition of the newborn (Table 4).

Table 1. Number of patients and analysed urine specimens in the five excretion groups

Excretion group	1	2	3	4	5	
Excretion of oestrone + oestradiol	Normal	Low	Normal-low	Normal	Low	
Excretion of oestriol	Normal	Low	Normal-low	Low	Normal	Total
Number of patients	20	11	9	9	3	52
Number of specimens	59	27	102	18	23	229

Table 2. Manifest or suspected abnormal clinical conditions of pregnancy in the five excretion groups. *Definitions:* Prolonged pregnancy: a gestation of more than 42 weeks. Toxaemia: at least two of the three signs: hypertension, oedema and proteinuria. Hypertension: a blood pressure of 140/90 or higher. Oedema: moderate to severe water retention. Anaemia: haemoglobin level below 80% (i.e. 12 g/100 ml plasma). Hæmorrhagia: all forms of vaginal bleeding. Hydrorrhoea: escape of amniotic fluid for more than 7 days

Excretion group	1	2	3	4	5	
Excretion of oestrone + oestradiol	Normal	Low	Normal-low	Normal	Low	
Excretion of oestriol	Normal	Low	Normal-low	Low	Normal	Total
Prolonged pregnancy	2	3	3	5	2	15
Toxaemia, hypertension	4	3	1	2	0	10
Oedema	5	4	2	3	0	14
Rhesus immunization	3	1	0	0	0	4
Anæmia	10	6	4	4	2	26
Hæmorrhagia	1	1	0	0	0	2
Hydrorrhoea	0	0	0	1	0	1
Addison's disease	0	1	0	0	0	1
Adrenogenital syndrome	1	0	0	0	0	1
Bad obstetric history	4	3	0	1	3	11
Other abnormal conditions	1	1	2	1	1	6

Table 3. Type of delivery in the five excretion groups

Excretion group	1	2	3	4	5	
Excretion of oestrone + oestradiol	Normal	Low	Normal-low	Normal	Low	
Excretion of oestriol	Normal	Low	Normal-low	Low	Normal	Total
Normal, vaginal	14	7	8	7	3	39
Forceps	0	1	0	1	0	2
Caesarean section	6	3	1	1	0	11

Table 4. Weight of the newborn and signs of foetal distress in the five excretion groups

Excretion group	1	2	3	4	5	
Excretion of oestrone + oestradiol	Normal	Low	Normal-low	Normal	Low	
Excretion of oestriol	Normal	Low	Normal-low	Low	Normal	Total
Birthweight > 2500 g	19	8	6	7	3	43
Birthweight ≤ 2500 g	2	3	3	2	0	10
Twins	2	0	0	0	0	2
Death *ante partum*	0	3	0	0	0	3
Death *in partu* (artificial)	0	0	0	1	0	1
Death *post partum*	0	0	0	0	0	0
Heartbeats affected *in partu*	1	1	0	0	0	2
Neonatal asphyxia	0	3	0	1	1	5
Dysmaturitas	1	1	1	2	0	5
Malformation	1	0	0	1	0	2
Erythroblastosis fetalis	3	1	0	0	0	4
Abnormal colour of amniotic fluid	1	5	0	1	1	8
Oligohydramnion (no fluid observed)	0	1	0	1	0	2
Hydramnion (≥ 1500 ml amniotic fluid)	0	1	0	0	0	1
Placental infarction	0	1	0	1	0	2

RESULTS

Identical type of excretion

Group 1. *Normal excretion of oestrone + oestradiol as well as of oestriol.* The excretion of oestrone + oestradiol and oestriol in these 20 patients is illustrated in Figs. 1 and 2 and the calculated oestriol/oestrone + oestradiol ratios in Fig. 3.

None of the infants died, but five infants were not normal at birth:

Case A: Birthweight 2600 g (37th week of gestation), erythroblastosis fetalis (rhesus), 3 exchange transfusions.

Case B: Birthweight 2300 g (34th week of gestation), erythroblastosis fetalis (rhesus), 6 exchange transfusions.

Case C: Birthweight 2900 g (37th week of gestation), signs of intrauterine asphyxia in birth, erythroblastosis fetalis (rhesus), one exchange transfusion.

Case D: Twin, birthweight 2900 g (36th week of gestation), cleft palate.

Case E: Birthweight 2000 g (the gestation age uncertain, probably 38th week), dysmaturitas.

The infants of the remaining 15 patients were healthy.

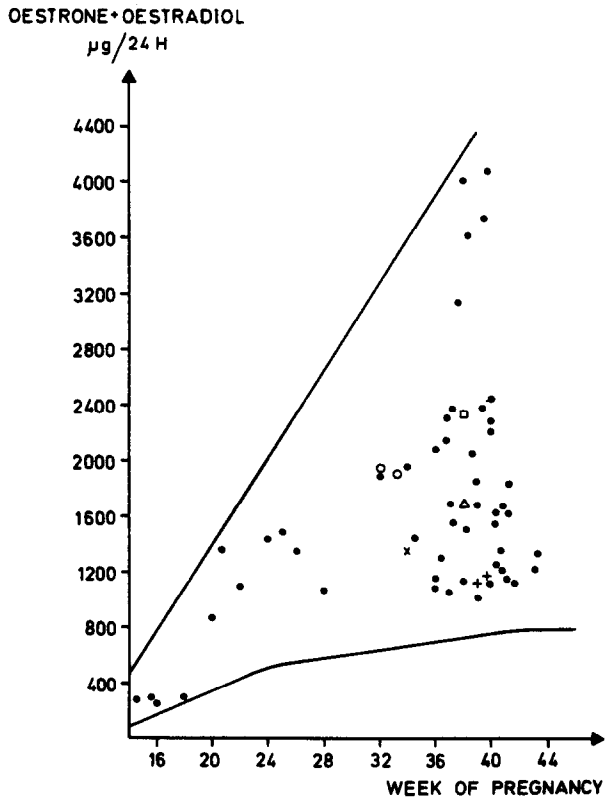

Fig. 1. Excretion of oestrone+oestradiol in the 20 patients of group 1. Oblique lines indicate normal limits[8]. Legend: ○ case A, × case B, □ case C, + case D, △ case E, ● the remaining patients.

In all patients, including cases A–E, oestriol/oestrone + oestradiol ratios were within normal limits.

Group 2. Low excretion of oestrone + oestradiol as well as of oestriol. The excretion of oestrone + oestradiol and oestriol in these 11 cases is illustrated in Figs. 4 and 5 and the calculated oestriol/oestrone + oestradiol ratios in Fig. 6.

In three patients the foetuses died *ante partum*:

Case F: Birthweight 880 g (30th week of gestation). Cause of death: probably erythroblastosis fetalis (rhesus). Several placental infarcts were present.

Case G: Birthweight 1200 g (33rd week of gestation). Cause of death: uncertain, but patient had toxaemia of moderate to high degree.

Case H: Birthweight 2350 g (37th week of gestation). Cause of death: unknown.

In three other cases the infants were asphyxiated after birth and many signs of foetal distress were present:

Case I: Birthweight 2600 g (43rd week of gestation). Infant showed signs of dysmaturitas and respiratory distress. No amniotic fluid was observed.

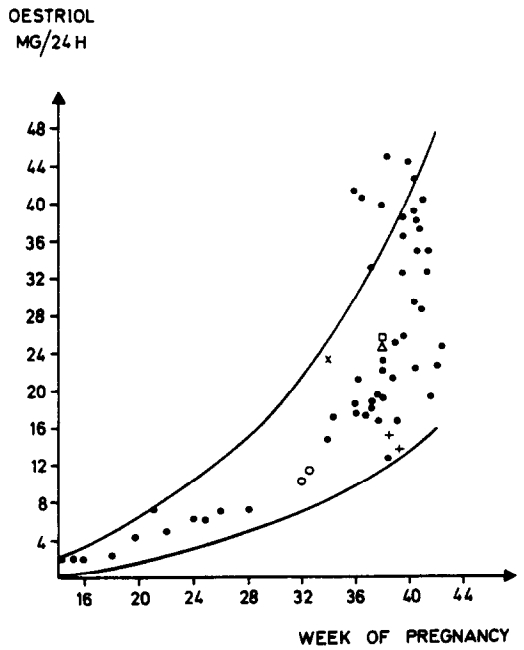

Fig. 2. Excretion of oestriol in the 20 patients of group 1. Oblique lines indicate normal limits[15, 16]. Legend: see Fig. 1.

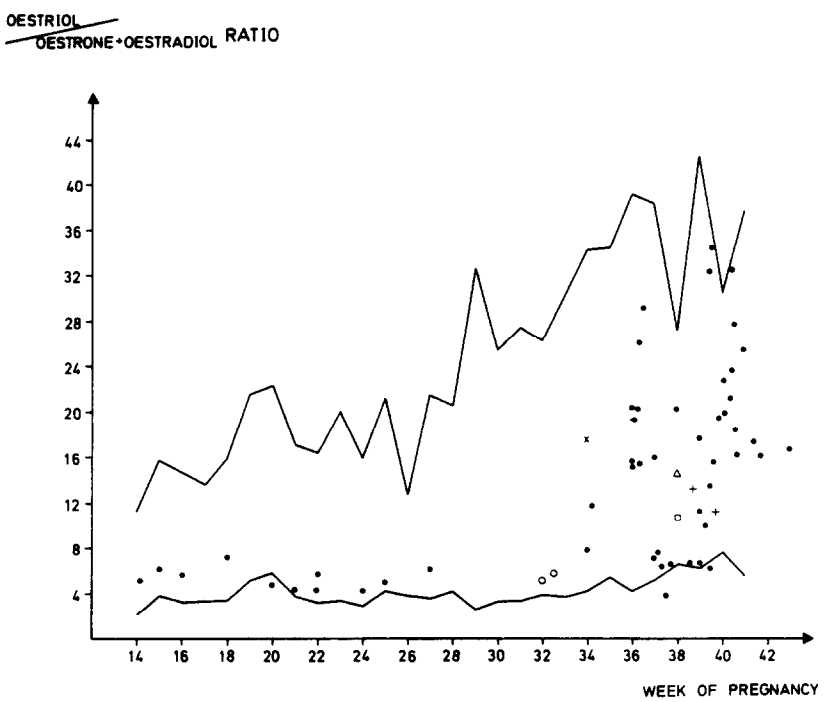

Fig. 3. Oestriol/oestrone + oestradiol ratios in the 20 patients of group 1. Oblique lines indicate normal limits[8]. Legend: see Fig. 1.

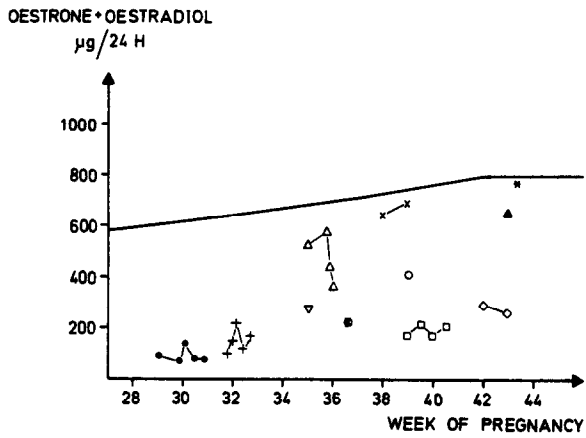

Fig. 4. Excretion of oestrone + oestradiol in the 11 patients of group 2. Oblique line indicates lower normal limit[8]. Legend: ● case F, + case G, ⊘ case H, ▲ case I, ▽ case K, × case L, ○ case M, △ case N, * case O, ◇ case P, □ case Q.

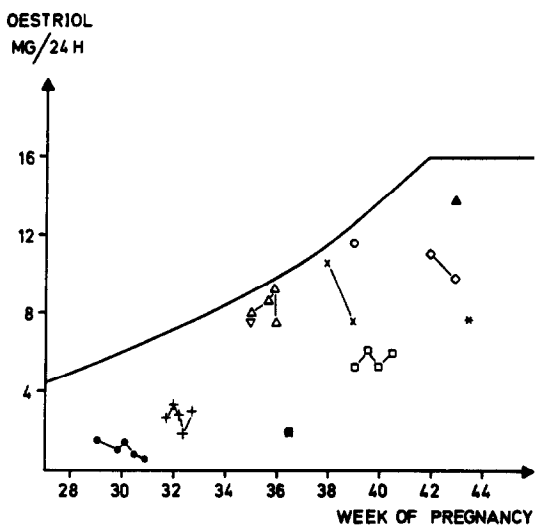

Fig. 5. Excretion of oestriol in the 11 patients of group 2. Oblique line indicates lower normal limit[15–17]. Legend: see Fig. 4.

Case K: Birthweight 3500 g (39th week of gestation). Infant severely asphyxiated after birth. Hydramnion was present, and after puncture of the membranes (1900 ml green fluid) the heartbeats were affected. Forceps were consequently applied.

Case L: Birthweight 3150 g (38th week of gestation). Infant asphyxiated the first days after birth. Patient had toxaemia; because of this and the low oestriol excretion Caesarean section was performed. The amniotic fluid was yellow.

The remaining five patients gave birth to mature and normal infants. The abnormal clinical conditions of these pregnancies were toxaemia (case M), bad

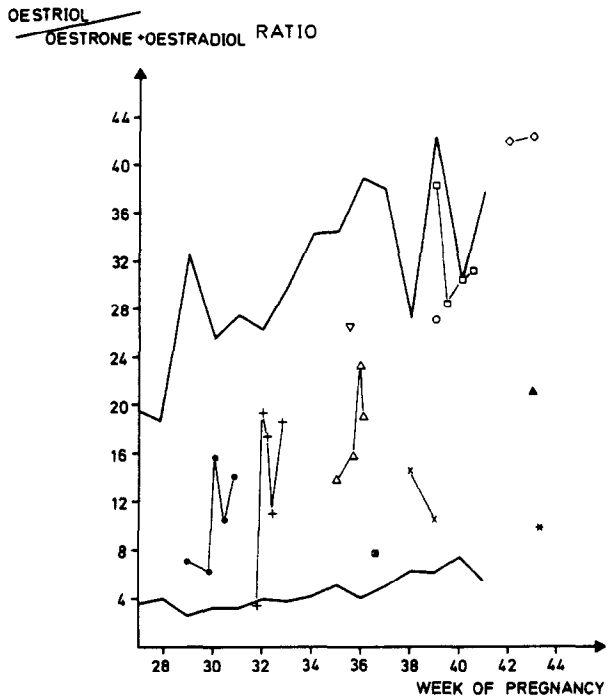

Fig. 6. Oestriol/oestrone + oestradiol ratios in the 11 patients of group 2. Oblique lines indicate normal limits [8]. Legend: see Fig. 4.

obstetric history (case N) and prolonged pregnancy (cases O and P). One patient with Addison's disease received cortisone and fluorocortisol, probably the cause of the low oestrogen output (case Q) [12].

The oestriol/oestrone + oestradiol ratios were high in cases P and Q, but otherwise no special tendency was seen.

Group 3. Excretion of oestrone + oestradiol as well as of oestriol characterized by a mixture of normal and low values. The excretion of oestrone + oestradiol and oestriol in these nine patients is illustrated in Figs. 7 and 8 and the calculated oestriol/oestrone + oestradiol ratios in Fig. 9.

Three infants showed signs of fetal malnutrition:

Case R: Birthweight 2250 g (43rd week of gestation). Infant showed signs of dysmaturitas. Pregnancy otherwise normal.

Case S: Birthweight 2500 g (44th week of gestation). Pregnancy otherwise normal.

Case T: Birthweight 2200 g (41st week of gestation). Pregnancy otherwise normal.

The remaining 6 patients gave birth to mature and normal infants. The complications of these pregnancies were prolonged pregnancy, terminated in the 44th week by Caesarean section (case U), hypertension (case V), ectopia renis and proteinuria (case Z), signs of praetemporarian labour earlier in pregnancy (case Ø) and oedema (cases Æ and Å).

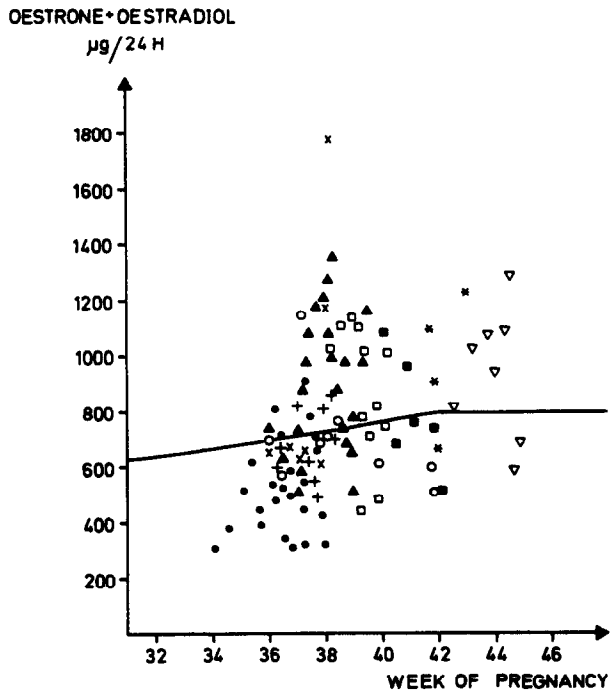

Fig. 7. Excretion of oestrone + oestradiol in the 9 patients of group 3. Oblique line indicates lower normal limit [8]. Legend: ■ case R, * case S, ○ case T, ▽ case U, × case V, ● case Z, □ case Æ, + case Ø, ▲ case Å.

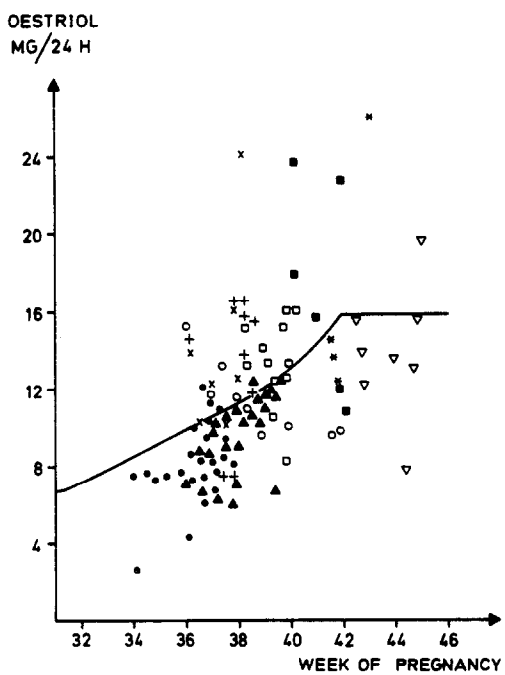

Fig. 8. Excretion of oestriol in the 9 patients of group 3. Oblique line indicates lower normal limit [15–17]. Legend: see Fig. 7.

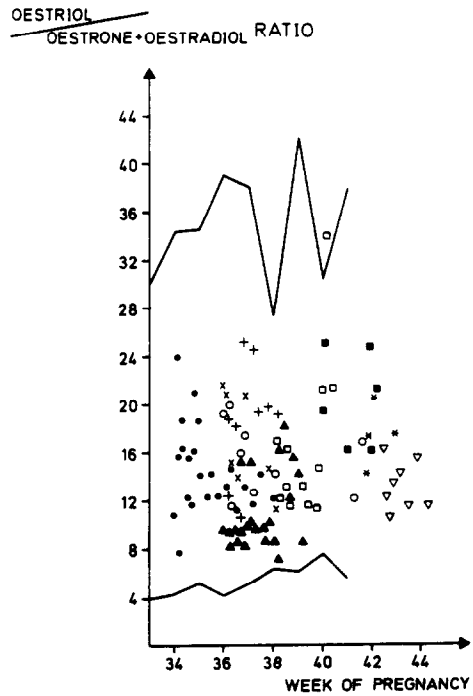

Fig. 9. Oestriol/oestrone + oestradiol ratios in the 9 patients of group 3. Oblique lines indicate normal limits [8]. Legend: see Fig. 7.

The oestriol/oestrone + oestradiol ratios were all within normal limits and no special tendency was seen.

Different type of excretion

Group 4. Normal excretion of oestrone + oestradiol, but low oestriol output. The excretion of oestrone + oestradiol and oestriol in these nine patients is illustrated in Figs. 10 and 11 and the calculated oestriol/oestrone + oestradiol ratios in Fig. 12.

One infant was still-born:

Case a: Birthweight 4250 g (40th week of gestation). Major degree of hydrocephalus diagnosed before delivery. Fetal death *in partu* in connection with artificial perforation of the cerebrospinal canal.

Three infants showed signs of foetal distress:

Case b: Birthweight 2300 g (43rd week of gestation). Signs of respiratory distress the first days after birth. Pregnancy complicated by hypertension.

Case c: Birthweight: 3200 g (43rd week of gestation). Infant showed signs of dysmaturitas. No amniotic fluid present.

Case d: Birthweight 1350 g (39th week of gestation). Infant showed signs of dysmaturitas. Hydrorrhoea present six weeks before delivery. Amniotic fluid meconium-stained. Pregnancy complicated with mild toxaemia.

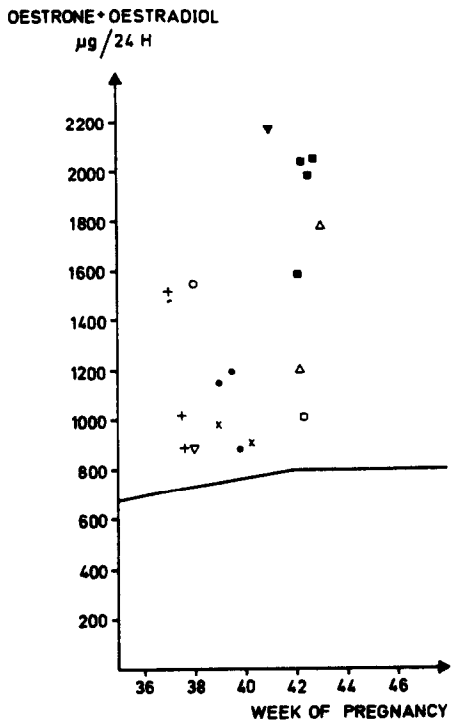

Fig. 10. Excretion of oestrone + oestradiol in the 9 patients of group 4. Oblique line indicates lower normal limit [8]. Legend: ● case a, ■ case b, ▼ case c, ○ case d, + case e, △ case f, × case g, ▽ case h, □ case i.

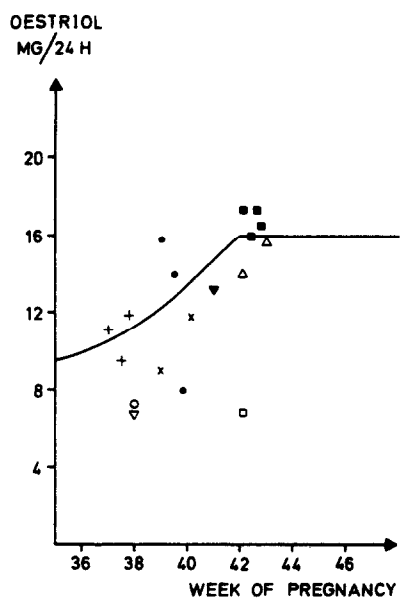

Fig. 11. Excretion of oestriol in the 9 patients of group 4. Oblique line indicates lower normal limit [15–17]. Legend: see Fig. 10.

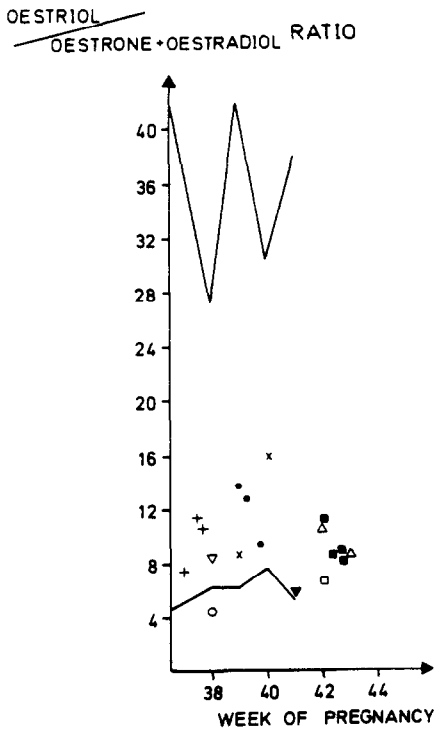

Fig. 12. Oestriol/oestrone + oestradiol ratios in the 9 patients of group 4. Oblique lines indicate normal limits [8]. Legend: see Fig. 10.

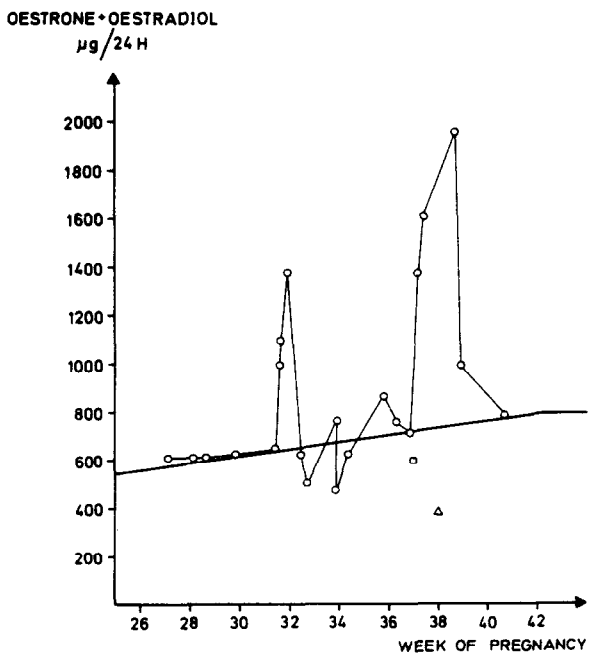

Fig. 13. Excretion of oestrone + oestradiol in the 3 patients of group 5. Oblique line indicates lower normal limit [8]. Legend: □ case j, ○ case k, △ case l.

The remaining five infants were mature and healthy. The abnormal conditions of pregnancy were bad obstetric history (case e), prolonged pregnancy (cases f, g and h) and infection of the urinary tract (case i).

The oestriol/oestrone + oestradiol ratios were relatively low, but in only one case (case d) below the lower limit.

Group 5. Excretion of oestrone + oestradiol low, but oestriol output normal. The excretion of oestrone + oestradiol and oestriol in these three cases is seen in Figs. 13 and 14 and the calculated oestriol/oestrone + oestradiol values in Fig. 15.

One infant was mildly distressed:

Case j: Birthweight 2800 g (37th week of gestation). Infant mildly asphyxiated the first days after birth. Amniotic fluid yellow. Patient had a bad obstetric history.

In the remaining two cases the infants were mature and healthy. The abnormal conditions of pregnancy were bad obstetric history and prolonged pregnancy (cases k and l).

The oestriol/oestrone + oestradiol ratios were all near or over the upper limit.

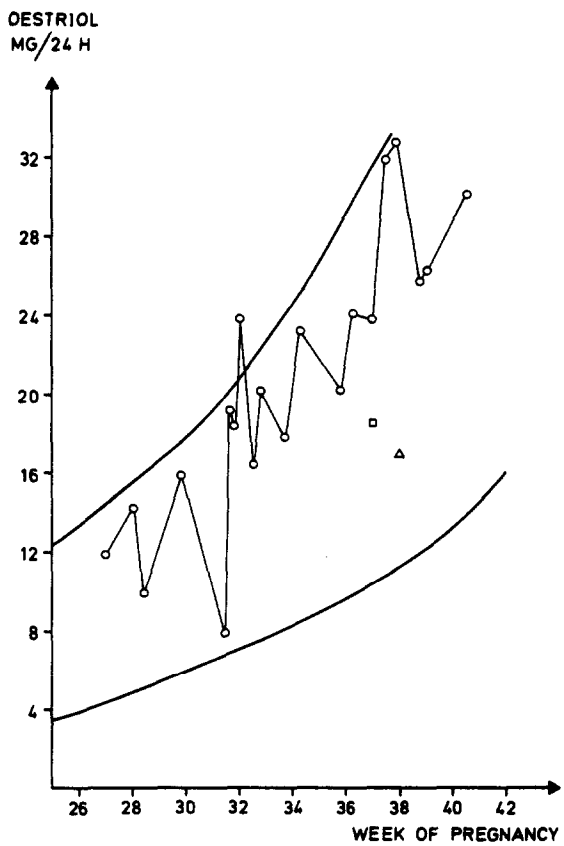

Fig. 14. Excretion of oestriol in the 3 patients of group 5. Oblique lines indicate normal limits [15, 16]. Legend: see Fig. 13.

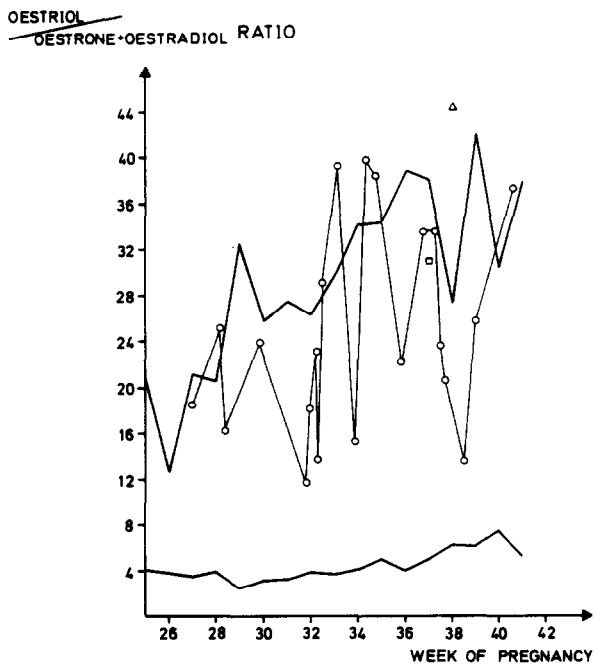

Fig. 15. Oestriol/oestrone + oestradiol ratios in the 3 patients of group 5. Oblique lines indicate normal limits [8]. Legend: see Fig. 13.

DISCUSSION

The main purpose of the present study was to evaluate the clinical significance of the oestrone + oestradiol excretion and the oestriol/oestrone + oestradiol ratio in pathological pregnancies, and in particular to throw light on this method used as a supplement to the oestriol assay.

The following discussion of this problem is based on the condition of the newborn.

Foetal death

Foetal death occurred in four cases.

Three infants died *ante partum* and in all cases the excretion of oestrone + oestradiol as well as of oestriol was very low (cases F, G and H).

A hydrocephalic infant died *in partu* for artificial reasons. The excretion of oestrone + oestradiol was normal, while the last of three oestriol values was below the lower limit. Of course a warning in this case of foetal death was impossible (case a).

Thus the present material suggests that the oestrone + oestradiol estimation can be used for diagnosing foetal death in the same degree as the oestriol method.

In all four cases the oestriol/oestrone + oestradiol ratios were within normal limits.

Retarded foetal growth

For definition we have accepted a birthweight of 2500 g or less at or after term.

Six cases belonged to this group.

In one patient neither the oestrone + oestradiol excretion nor the oestriol output was reduced. The gestational age was uncertain, but the infant, weighing 2000 g, was dysmature (case E).

In the remaining five patients the oestriol output was reduced in all cases, while the excretion of oestrone + oestradiol was lowered in only three of these patients (cases R, S and T). In the other two cases the oestrone + oestradiol values were normal in spite of signs of foetal distress (cases b and d).

Thus for diagnosing retarded foetal growth one has to prefer the oestriol to the oestrone + oestradiol excretion. In no case did the oestrone + oestradiol values or the oestriol/oestrone + oestradiol ratios give information not obtainable by the oestriol assay.

Other signs of disorder of the infants

Six patients belonged to this group.

In one case neither the oestrone + oestradiol excretion nor the oestriol output was reduced, but a warning of cleft palate in a twin-pregnancy could not have been expected (case D).

In three cases complicated with neonatal asphyxia the excretion of oestrone + oestradiol as well as of oestriol was reduced (cases I, K and L). Furthermore in cases I and K other signs of fetal malnutrition were present (dysmaturity, oligohydramnios, meconium-stained amniotic fluid and bad heartsound *in partu*).

In the two remaining patients the excretion of oestrogens was different. In one case the oestrone + oestradiol excretion was reduced and the oestriol output normal. The amniotic fluid was yellow stained and the infant had a mild neonatal asphyxia (case j). In the other case the oestriol excretion was low and the output of oestrone + oestradiol normal. Oligohydramnios was present and the infant, weighing 3200 g, showed signs of dysmaturity (case c). However, in each of these two cases only one estimation was performed.

Thus it can be said that in this group the clinical significance of the oestrone + oestradiol output was not essentially different from that of the oestriol excretion.

The oestriol/oestrone + oestradiol ratios of this group were all within normal limits.

Erythroblastosis fetalis

The excretion of oestrone + oestradiol as well as of oestriol was normal in three cases complicated with moderate to severe erythroblastosis fetalis because of rhesus incompatibility (cases A, B and C). It is well known that oestriol assays are of little prognostic value in such pregnancies [13]. and apparently no further advantage can be derived from estimating the excretion of oestrone + oestradiol.

The oestriol/oestrone + oestradiol ratios were normal in these cases.

It deserves notice, that in the fourth patient with rhesus-immunization antenatal foetal death occurred. However, all estimations were obtained after the time of foetal death (case F).

The results of the present study indicate that the oestrone + oestradiol assay can be used by the clinician in the assessment of the foeto-placental function. However, the clinical significance of the oestriol estimations appeared to be better, especially concerning the diagnosis of retarded foetal growth.

Neither the oestrone + oestradiol assay nor the oestriol/oestrone + oestradiol ratios provided essential information not obtainable by means of the oestriol

estimations. Thus a combined employment of the two methods does not seem to give further advantage to the clinician.

The production of oestriol appears to be more sensitive to changes in the foeto-placental unit than that of oestrone + oestradiol. Apparently the oestriol excretion is 'falsely low' in some cases. However, the cause may be pathological changes in the foetus not disclosed by means of a clinical judgement of the infant during the first week of life. It is not advisable to rely upon a normal oestrone + oestradiol output in these cases.

From a clinical point of view further investigations are therefore still required to clear up the significance of other oestrogen compounds from the foeto-placental department.

Another conclusion interesting from an academic point of view, which can be derived from this study, is that the production of oestrone + oestradiol during pregnancy is limited by the same factors as the production of oestriol, namely the output of precursors from the foetal adrenals. Consequently the 16-hydroxylation, probably taking place mainly in the foetal liver, can be ruled out as the limiting factor, except in the rare cases where severe foetal liver damage is present [14].

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