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URINARY OESTRIOL IN PREGNANCY

Review

by

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Even before the First World War certain German workers had noted the presence of oestrogenic substances in the human placenta, and Fellner (1912) is generally credited as being the first to make this observation. In the following decades, it became obvious that the placenta was indeed a rich source of oestrogenic materials and by 1930 pure oestriol had been identified in extracts of the human placenta.

It was not until 1927 that the German workers, Aschheim and Zondek, made the astonishing discovery that the urine of certain pregnant animals contained amongst many other substances oestrogens in large quantities. In the same year they noted the presence of large quantities of oestrogenic substances in human pregnancy urine and in the following year demonstrated that the oestrogens in the human pregnancy urine rose from the 12th week of pregnancy to relatively high levels at term to fall to low levels in the early puerperium. In 1927, Margaret G. Smith demonstrated that the blood of pregnant human females contained a substance identical with "Follicular hormone" and this reached its maximum concentration at term, only to disappear rapidly in the puerperium.

It is worth remembering, then, that over 50 years ago it was known that the placenta was a rich source of oestrogens and that these substances appeared in the blood and urine in increasing quantities until term and they promptly disappeared following delivery. All this painstaking work had of course been dependant on

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biological methods of estimating oestrogens.

In 1933, Spielman, *et al,* utilizing a biological assay for oestrogens in blood, found that this procedure could be used as an early and reliable clinical indicator of whether the foetus is dead or alive. One mouse-unit of oestrogen in 40 ml. of blood indicated foetal life as early as 8 to 10 weeks' gestation. A sudden drop of the oestrogen titre in maternal blood occurred when foetal death took place. This method did not gain wide acceptance in clinical practice because of large quantities of blood necessary and the difficulties of biological assay.

In the same decade, Smith and Smith used a biological assay and demonstrated a decreased production of oestrogen and an increased production of chorionic gonadotrophin in pregnancies complicated by pre-eclampsia, eclampsia, premature, delivery and stillbirth. A progressive deficiency of oestrogen was found in a large number of instances. It was further noted in a toxaemic patient under treatment with veratrum viride that the vasodilating action of this drug was accompanied by a temporary reversal of the urinary deficit indicating more normal secretion and metabolism of the steroid hormones.

Bachman, in 1941, published his findings on six gravid women in whom serial chemical determinations were made of oestradiol, oestrone, oestriol and pregnanediol. The oestrogen determinations were performed by a colorimetric method developed by him. This work was carried out primarily to determine whether any relation could be demonstrated in the excretion of these compounds and the onset and character of labour. It was concluded that no constant hormonal excretory patterns were observed in this respect. The changes in oestrogen output during the last ten weeks of pregnancy were too gradual and the individual variations among different patients too marked to make any possible forecast on the day when labour would begin or the character of the labour. However, it is very interesting to note in this thorough study of six patients that patient No. 6 was normal throughout pregnancy except for a labile blood pressure, which rose to moderate hypertensive levels. The hormonal excretions of this patient were so markedly below those of the remaining patients that Bachman stated that further hormonal studies during pregnancy should be conducted.

Zondek and co-workers (1954, 1957 and 1959), have done extensive studies on the use of urinary oestriol excretion in the abnormalities of pregnancy. They concluded that the urinary oestrogen titre, as determined by biological assay, did not lead to conclusive results in the assessment of placental function, but a chemical determination of urinary oestriol can give valuable information. The preference for a chemical rather than bio-assay procedure is based on the following. The oestrogens of pregnancy include oestrone, oestradiol-17B and oestriol. Oestriol constitutes the main bulk (90%) of the total urinary excretion on the basis of weight. Oestriol is physiologically a very weak oestro-

gen that possesses a biological activity approximately 1/100 that of oestrone and 1/500 that of oestradiol-17B, depending upon the type of biological assay performed. Therefore, a small contamination of the final oestriol fraction by oestrone or oestradiol could greatly influence the values obtained by bio-assays, and falsely imply changes in oestriol excretion quite disproportional to the gravimetric content of this fraction.

In order to overcome this difficulty. Zondek *et al*, employed the chemical procedure of Finkelstein (1952) for the determination of urinary oestriol alone. Utilizing this procedure, the oestriol assay was found reliable in the detection of placental dysfunction after the 20th week of pregnancy.

During the last trimester of pregnancy, the daily variation by their method may be considerable (up to 60%). Fluctuations in the urinary oestriol indicate dysfunction of the placenta, a rising titre indicating reversible placental dysfunction. Fluctuations occurred more frequently in toxaemic pregnancies than in normal cases. A fall of over 60% is considered as prognostically unfavourable and treatment should be influenced by this in combination with other clinical criteria. The absolute oestriol value is of importance. Oestriol level remaining below 1 mgm. per 24 hours indicates irreversible placental dysfunction and secondary death of the foetus, while levels below 3 mg. per 24 hours reflect imminent danger to the foetal life. In toxaemia of pregnancy there is a tendency for increased excretion of chorionic gondotrophin with decrease in oestrogen excretion. This was found in about 25% of the instances.

The work of Taylor *et al* (1958) using a chemical method of Anker (1955), suggested that in patients who had premature labour there was a low level of total urinary oestrogens, and in severe pre-eclampsia urinary oestrogens were also low. These studies seemed to indicate that there was placental dysfunction as measured by the total urinary oestrogen output, and that oestriol excretion was related to foetal weight.

Lanters (1958), in an extensive study of oestriol excretion in toxaemia of pregnancy, demonstrated that in mild cases normal oestriol values were usually found, but when the blood pressure was at high levels the oestriol tended to be lower. In severe cases of toxaemia oestriol excretion was abnormal and did not increase as pregnancy advanced. He found good correlation between the histological appearance of the placenta and oestriol excretion and also between placental weights, foetal weights and oestriol excretion.

Keller *et al* (1959), studied urinary oestriol excretion by Brown's method (1956). They established values in normal pregnancy at different periods of gestation and put forward the 'Edinburgh curve'. They corroborated the evidence that in toxaemia of pregnancy urinary oestriol estimation may prove a valuable guide as regards placental function. It is interesting to note that a patient, who was originally included in the normal series at the beginning of her pregnancy, later developed toxaemia and she had a falling oestriol excretion 'some little time' before she de-

veloped pre-eclampsia at 33 weeks. This fall in oestriol excretion before the clinical onset of toxaemia has also been observed by the present author in one of his cases.

Ten Berge (1959, 1960) carried out an extensive study of urinary oestriol and found this test a useful clinical tool. A progressive decline in oestriol excretion was associated with increased placental degeneration. Decreased oestriol excretion was associated with appearance of fibrin in the villous spaces, clotting of villi, appearance of oedema and necrosis in the stroma of the villi and the formation of thrombi in the vessels. In his series of patients, oestriol excretion was determined either daily or at least every second or third day, and in this way a guide provided to indicate when pregnancy should be terminated in toxaemia, hypertension or diabetes mellitus. There was good correlation among the clinical aspects, microscopic and macroscopic features of the placenta, perinatal mortality, foetal weight and urinary oestriol excretion. They cite some specific levels: values below 10 mg. per 24 hours indicate a real danger to foetal life. It is a bad sign when oestriol values do not rise in the last trimester. With values below 10 mg. per 24 hours, preference should be given to caesarean section as a means of delivery. With levels around 15 mg. per 24 hours delivery per vaginam may be permitted in favourable circumstances. Daily oestriol values fluctuate and a fall should be judged by at least 2 estimations ; with intrauterine death oestriol values fall abruptly to very low levels.

Frandsen and Stakemann (1960), utilising their own method to determine urinary oestriol showed that in 20 women with normal pregnancies, examined weekly, the amounts of oestriol excreted varied greatly from individual to individual. At term the range was 16-25 mg. per 24 hours. A positive correlation was found between the oestriol excretion at term and the weight of the baby. It was demonstrated that when foetal death occurred, the amounts of oestrogen in the maternal urine dropped to low levels that are never found when the foetus is alive. It was demonstrated that foetal stress can be accompanied by decreased urinary excretion of oestriol. Serial urinary analysis warns the clinician that the foetus is in danger, a moderately decreased excretion indicates impending danger to the foetus, and an extremely low value means that the foetus has died. The proper time for the termination of pregnancy could be determined by serial urinary oestriol determinations. Ten cases of postmaturity were studied, five were found to have a low output of oestriol.

Greene, Touchstone and Fields (1961, 1962, 1963), studied the urinary oestriol excretion as an index of placental function in a large series of patients, using a chemical procedure. The following results were reported: when maternal urinary oestriol values of 12 mg. per 24 hours and above were found within 24 hours of delivery, no foetal mortality occurred, except in instances of erythroblastosis foetalis. In cases of erythroblastosis foetalis, no correlation could be established between oestriol excretion and the condition of the foetus. During the third tri-

mester, no infant survived that remained in utero for 2 days or more when values of less than 4 mg. per 24 hours were found. Furthermore, it was reported that oestriol excretion between 4-12 mg. per 24 hours may represent foetal jeopardy, depending upon the stage of gestation. No intrauterine foetal death occurred when values between 4-12 mg. per 24 hours were obtained, but 10 babies died in the neonatal period when the maternal oestriol was between 5-9 mg. per 24 hours before delivery. Twenty-six infants, whose delivery was indicated because of falling titre of oestriol, survived. It was concluded that infants at or near term may be salvaged by timely delivery in the presence of low values or rapidly falling urinary oestriol levels, provided daily determinations are carried out to show the decrease in the excretion. Delivery of some infants could be deferred to achieve greater maturity in complicated pregnancy when daily oestriol values indicate that intra-uterine foetal death was not imminent.

Banerjea (1962), studied the total urinary oestrogens by Ittrich's modified method (1960) and concluded : 'In comparison with the other available methods for the determination of placental function, urinary oestrogen estimation appears to be superior on most counts. It is of distinct value as an ancillary aid to the clinician dealing with pregnancy complicated by toxaemia, essential hypertension, diabetes, nephropathies etc.'

Coyle *et al* (1963), using modified Brown's method (1963), carried out urinary oestriol estimation in cases of normal pregnancy and various pregnancy complications. They reported a fair correlation between the oestriol values before delivery and foetal weight at birth.

Wray and Russel (1963), using modified Brown's method (1957), established the curve for normal pregnancy. They warn that "the range of excretion is wide and caution is advised in interpreting falls in excretion as meaning the foetus is in danger".

Wakhaloo and Dhall (1964, 1966), studied urinary oestriol excretion in 137 cases including cases of normal pregnancy and various abnormalities of pregnancy, using the method of Eberlein Bengiovanni and Francis (1958) with certain modifications. The values in normal pregnancy obtained in this series are shown in Table 1.

TABLE I

Urinary oestriol values in normal pregnancy
(Wakhaloo and Dhall, 1964)

Weeks of gestation	Maximum mg./24 hours	Minimum mg./24 hours	Mean mg./24 hours
20	5	3	4.37 ± 0.94
30	15	5	10.02 ± 3.78
35	25	7	15.86 ± 3.69
40	31	15	22.10 ± 4.16

They compared the values in normal pregnancy obtained by different workers and concluded that the pattern of oestriol excretion was the same, though the values differed slightly depending upon the method employed.

The patients whose values were within the normal zone gave birth to healthy infants and there was no stillbirth or unexplained neonatal death. Oestriol value below 8.5 mg. per 24 hours after 35 weeks of gestation was associated with high perinatal mortality and cases where value was below 2.5 mg. per 24 hours during the last 5 weeks of gestation delivered stillborn babies, either fresh or macerated. There was good correlation between the amount of oestriol excreted and the weight of the baby.

It has been remarked that owing to the wide variation of results from patient to patient and also the significant daily variation in the same patient, a single low value is not of much importance except as an indication to repeat the assay. Values which are falling, persistently low or show a persistent fall from a previous high value, are suggestive of placental insufficiency and early intervention may save some babies in such cases. They conclude that urinary oestriol assay is a reliable method of assessing placental function and the clinician should make more wider use of this method in addition to the clinical parameters.

Breborowicz *et al* (1965) tried to investigate the relationship between the structure of the placenta and the amount of urinary oestrogen. As a possible morphological basis for the production of oestrogens, the general amount of the placental tissue, expressed by the weight of the placenta and the percentage of the syncytium in the placenta, was determined. One hundred and sixty-five cases including cases of normal pregnancy, post date pregnancy, pregnancies complicated by toxaemia, diabetes mellitus or Rh incompatibility, foetal malformations were studied. It was concluded that there exists a relationship between the urinary oestrogen and the weight of the placenta. They point out that there are other factors also, like the presence and the amount of degenerative changes in the placenta, which influence the excretion of oestrogens. They could not find any relationship between the amount of oestrogen excreted and the percentage of syncytium in the placenta. It is remarked that in the production of oestrogen, the function of the placenta is not autonomous but depends on the state of the foetal adrenals.

Greene *et al* (1965) evaluated the use of urinary oestriol excretion in the management of pregnancies complicated by diabetes mellitus. They followed 88 patients from 28 weeks of gestation and samples were assayed at frequent intervals. It was concluded that frequent measurements of urinary oestriol will permit a marked reduction in the intrauterine foetal loss in such cases, since intrauterine death is invariably preceded by a fall in oestriol excretion. They recommended serial urinary oestriol assay as an integral part of antenatal care in pregnancies complicated by diabetes mellitus. When normal amounts of oestriol are excreted,

there is no risk to the foetus and the patient may be allowed to carry her pregnancy to a greater degree of maturity. When consistently low or falling values are encountered, marked intrauterine jeopardy exists and the pregnancy should be terminated if the foetal size is adjudged adequate to indicate a reasonable chance of neonatal survival.

Carrington from Philadelphia, commenting on this paper, remarked that the policy of mandatory delivery of insulin-dependent diabetic mothers during the 36th week (earlier if other complications exist) has recently undergone revision in many clinics. It has been noted by several groups that when the perinatal mortality of 10-15 per cent is achieved, stillbirths are less frequent. Too often extrauterine death is substituted in the attempt to forestall the disaster in utero. Serial 24-hour urinary oestriol determinations can be of help in such cases.

Smith *et al* (1966), used urinary oestriol assay in the diagnosis and management of 67 cases of prolonged pregnancy. High levels were found in patients who delivered healthy mature infants, whereas levels less than 4 mg. per 24 hours signalled foetal death and in one case a severely affected infant was born with probable residual neurological damage. About one-third of these cases fell into the border line range of oestriol (between 4 to 12 mg. per 24 hours) and half of these delivered infants showing signs of 'postmaturity syndrome'; except for 2 infant deaths, all the affected babies in this group survived in the nursery. They performed 8 caesarean sections in the borderline group; 3 because foetal distress occurred following onset of spontaneous labour, one because of foetal distress during attempted induction; the other 4 sections were done because the oestriol levels dropped to borderline levels from previous high values. In this series of 67 cases, 41 were primigravidae, 18 were over the age of 30 and among those giving birth to babies showing 'postmaturity syndrome' 7 were elderly primigravidae, thus upholding the contention that prolonged pregnancy is more dangerous in elderly primigravidae.

Lundwall and Stakemann (1966) investigated urinary oestriol excretion after 42 weeks of gestation in 171 cases. They considered excretion of 16 mg. per 24 hours as the lower limit of normal values. The oestriol values in their cases are shown in Table II.

TABLE II

Urinary oestriol excretion in post-maturity
(Lundwall and Stakemann, 1966)
Number of cases with normal and abnormal oestriol excretion

Weeks of pregnancy	42nd	43rd	44th	45th	46th and 47th
Normal oestriol excretion	21	48	36	13	16
Low or declining oestriol excretion.	2 (9%)	6(11%)	15(29%)	8(39%)	6(27%)

It is evident from this table that the percentage of pregnancies with a low or declining excretion of oestriol increased with the length of gestation. All 135 patients with normal excretion of oestriol delivered healthy babies, except one where the baby died 10 days after birth due to congenital heart disease. In cases with excretion levels less than 16 mg. per 24 hours, foetal distress was not evident in every case but a large proportion did show some evidence. They conclude that pregnancy should be allowed to continue with values over 16 mg. per 24 hours. If decreasing values or values less than 16 mg. per 24 hours are obtained, the whole situation should be reviewed and in most cases the pregnancy should be interrupted. In patients with severely impaired oestriol excretion, caesarean section should be preferred to induction of labour.

Yousem *et al* (1966), measured oestriol excretion in 12 pregnant women manifesting clinical evidence of dysmaturity. In 11 they found diminishing values. They remark that in attempting to utilize the maternal urinary oestriol as an index of foetal health, one must take into consideration the various factors that influence the values of this hormone. A few known are: duration of pregnancy, diuresis, impending premature labour, renal or hepatic disease present in the mother and glycosuria.

Schindler *et al* (1967), did oestriol determinations in pregnancies complicated by Rh-isoimmunisation in three compartments: viz. amniotic fluid, maternal plasma and urine. They concluded that the urine and plasma oestriol levels do not reflect the condition of the erythroblastotic foetus, but they found low amniotic fluid oestriol levels in severely affected foetuses. They recommended oestriol assay in amniotic fluid as an additional safeguard in the management of Rh-isoimmunised patients.

Beischner *et al* (1967), studied urinary oestriol excretion in 63 cases of antepartum haemorrhages. Normal values were obtained in 13 out of 14 cases of placenta praevia, the fourteenth patient delivered an anencephalic baby where low values are known. Low values were obtained in 30 of the 49 cases with other causes of antepartum haemorrhage. Oestriol values were low in 15 of the 19 cases of accidental haemorrhage including 4 patients whose pregnancies resulted in foetal deaths. Among 22 patients having antepartum haemorrhage of unknown cause, 11 had low values including 4 out of the 8 patients with circumvallate placenta. Although none of them showed clinical signs of accidental haemorrhage, there were 4 in whom retroplacental clots were found. They believe that placental insufficiency should be excluded by oestriol determination before any patient with antepartum haemorrhage is allowed to go home. It is concluded that oestriol measurements have a useful place in the management of patients with antepartum haemorrhage.

From the study of literature it can be concluded that urinary oestriol assay is a reliable index of placental function except in cases of Rh-isoimmunisation, and it should be used more widely. Popularisation of this aid presents certain problems:

1. Apart from the foeto-placental

unit, there are various maternal factors, known and unknown, which influence the metabolism and excretion of oestriol and make interpretation of the results difficult. This would demand further studies with regard to the metabolism of oestrogens in pregnant women.

2. The techniques available at present for the assay are laborious and complicated. No doubt many improvements have taken place in the last few years but popularisation and wider use of this aid would require further simplification of the technique.

3. It is difficult to collect 24 hours urine sample from patients who are not hospitalised. It would be worthwhile if assay could be performed on a random specimen or a specimen of shorter period. Dickey *et al* (1966) have evaluated the diurnal excretion of oestrogen and creatinine during pregnancy. They claim that the oestriol-creatinine ratio can be obtained from analysing a random urine specimen and that this ratio is more or less constant in the same patient in the absence of any interference in renal clearance. This is based on the assumption that creatinine excretion is more or less constant in a particular patient and the factors governing the renal clearance of oestriol and creatinine are the same. The evidence so far is inconclusive and the matter is still open. Besides, one has to remember that the kidney does not go 'scot free' in complications of pregnancy like toxaemia, hypertension and chronic nephritis where oestriol assay is of value in the diagnosis of placental insufficiency.

In preparing this review an attempt has been made to collect as much material as was possible. No doubt the work of many authors must have been missed, but this in no way minimises their contribution to this important and fascinating topic in obstetrics. My thanks are due to Professor P. K. Devi, M.S., F.R.C.S., for her valuable suggestions in preparing this paper.

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