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A CLINICO-PATHOLOGICAL ASSESSMENT OF THE VALUE OF URINARY OESTRIOL ASSAYS DURING THE THIRD TRIMESTER OF PREGNANCY*

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An objective assessment of placental function, which will improve on clinical assessment, remains one of the more urgent problems in obstetrics. The placenta has several different functions, so that selection of one function which is being tested for by a technique designed to test that function, need not necessarily be representative of total placental function. In addition it is not only the placenta as such which is involved. There are essentially maternal, placental and foetal elements to take into account. That this is so, was well illustrated by Cassmer[5] and Diczfalusy *et al.*[7,8]

It is now a well-established fact that satisfactory progress in pregnancy is on the whole characterized by higher urinary oestriol values, whereas an unsatisfactory clinical course from the point of view of renal-hypertensive placental insufficiency, tends to have lower values. One of the best examples of the excretion levels of oestriol for various stages of pregnancy was depicted in 215 cases by Banerjea[1] using Ittrich's[9] modified method. The over-all validity of these excretion levels which he gave, was substantiated in our much smaller series.

The main aim of the present study was to determine the value and the place in the individual patient of maternal oestriol excretion as an index of placental-foetal function. Is it more accurate and does it give earlier indication of placental insufficiency than the clinical assessment? Which are the groups in whom the greatest value will be obtained? How do these oestriol values correlate with the decidual spiral arterial and placental findings?

MATERIALS AND METHODS

Thirty pregnant patients were studied. They were taken at random to include cases with mild to severe renal-hypertensive disorders, primiparae, multiparae, systemic lupus erythematosus and unexplained perinatal loss. No cases of diabetes or erythroblastosis foetalis were included.

They were all admitted to hospital and kept in bed for at least 24 hours before and during the urine collections. Full separate records were kept and a number of additional investigations done on most of them.

A rapid method of estimating urinary oestriol excretion was described by Montagu.[12] He compared this quick technique extensively with that of Brown,[3] Cartlidge *et al.*[4] and Coyle and Brown,[6] and found that it gave entirely satisfactory results.

The method presently employed for the determination of urinary oestriol is that of Montagu,[12] with modifications in the volumes of urine and of reagents, introduced to improve the reliability of the procedure. To 1 ml. of urine is added 10 ml. of hydrochloric acid and it is then extracted twice with 15 ml. of diethyl ether. The extracts are added to 40 mg. of dried hydroquinone; 2 ml. of sulphuric acid are added, diluted with 3 ml. of water, and finally 4 ml. of p. nitrophenol is added for the colour reaction.

The characteristics of the modified method were as follows:

Sensitivity. The lowest limit of measurement was 0·5/μg. oestriol = 1 mg. per 24 hours, assuming 2,000 ml. excretion.

Specificity. No reasonable values for oestriol were observed in urinary specimens from adult male patients, while specimens from non-pregnant women or from pregnancies of less than 12 weeks duration contained less than 0·5 mg. oestriol per day. Non-oestrogenic urinary constituents did not, therefore, interfere with the assay, but the presence of glucose lowered recoveries of oestriol.

Reproducibility. The coloured product given by oestriol with p. nitrophenol was unstable, and readings were all made within 10 minutes of adding p. nitrophenol. Optical density measured in the Beckman D.U. Spectrophotometer showed very good linearity against oestriol concentration throughout the range 0·5 - 40 μg. Six determinations of the oestriol concentration of portions of the same urinary specimen gave optical density readings in the range 0·141 - 0·162, mean 0·154.

Recovery. When compared with oestriol standards, oestriol, added to male, sugar-free urine and carried through the entire procedure, gave an over-all recovery of 73%.

The placentas were all examined by myself. The histological preparations were all stained with haematoxylin and eosin. They were all assessed by myself without previous knowledge of the patient's history or her oestriol assay results. As it is the main aim of the present investigations to assess the value of this test in the individual patient, a few representative cases were selected for individual analysis and assessment.

CASE HISTORIES

Case 1

This 30-year-old primipara booked for her confinement at 22 weeks. At this stage her blood pressure was 130/90 mm.Hg. She was managed as an outpatient until 20 September 1964, at which time the blood pressure had risen to and remained at 150/95 mm.Hg and slight oedema of the ankles was found. She was clinically estimated to be 35 weeks pregnant.

Admission to hospital on 20 September prevented a deterioration in her condition, but it was thought inadvisable to allow her to progress with pregnancy beyond 38 weeks. Surgical induction plus pitocin drip failed to establish labour, and caesarean section was performed when the blood pressure rose to 170/115 mm.Hg and the temperature to 101·4°F. A live male child of 6 lb. 6 oz. was delivered, with an Apgar rating of 1. He was resuscitated successfully. The placenta was normal.

Interpretation. Though the oestriol readings are variable, they are well within the ranges of normal and showed a rising tendency towards term (Fig. 1), despite a maintained blood pressure of about 150/100. The last reading was not available when the induction was performed. Though there are some obstetricians who would not have induced the patient at 38 weeks, I think I am correct in saying that consensus of opinion favours the induction approach.

Induction would have been performed even if the last oestriol result had been available. The potential danger in this type of patient was brought to light by a rise in blood pressure to 170/115 mm.Hg during labour. Thus, vigilance for potential catastrophe should be maintained despite a rising oestriol level.

The placental and foetal functions and growth were thus clinically adequately maintained and the oestriol estimations proved to be irrelevant to the management of the patient.

Case 2

This 43-year-old patient, who was gravida 9 and para 8, had had one stillbirth (her 6th child), the cause being unknown. Babies' weights varied between 6 and 9 lb.

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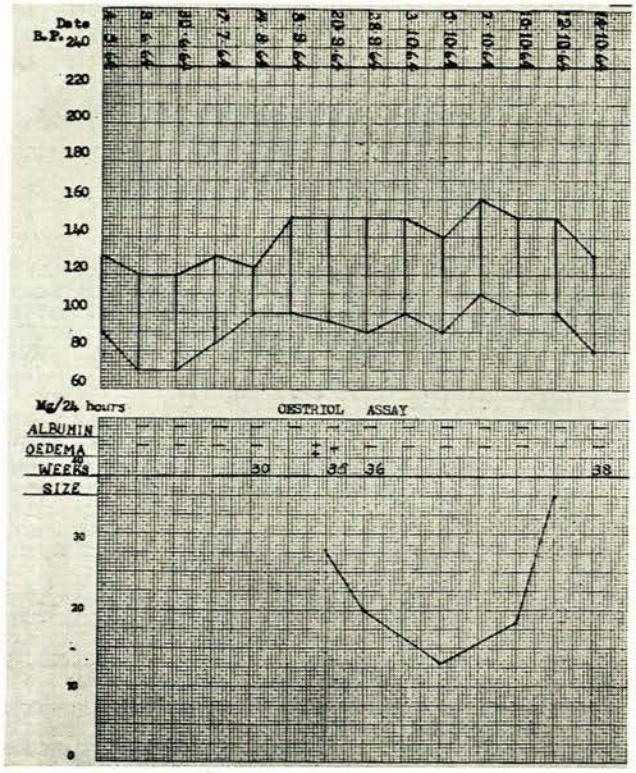

Fig. 1. See text.

She booked for her confinement on 20 September 1964, having at that time a blood pressure of 180/110 mm.Hg. She was then clinically estimated to be 31 weeks pregnant. Her weight was 211 lb. Her blood pressure dropped after undergoing rest in bed and was maintained at a somewhat lower level. Foetal growth progressed satisfactorily and the oestriol excretion continued to rise. Induction was carried out at 39 weeks and a baby weighing 8 lb. 2 oz. was born.

Interpretation. In this older, multiparous, mild to moderately hypertensive group of patients with a previous obstetrical history not suggestive of chronic placental insufficiency, it is relatively uncommon to be suddenly confronted with it. There is nearly always clinical evidence of deterioration in those who appear to have placental insufficiency.

Termination of pregnancy was indicated on the clinically accepted grounds that extra-uterine existence carries with it a better prognosis than intra-uterine life beyond 38 weeks under these circumstances. Thus, induction was indicated despite a rising oestriol excretion.

The normal oestriols (Fig. 2) reflected the functions of a normal-sized baby and a placenta of 18 oz., which was normal macroscopically and microscopically with regard to spiral arterioles, decidua, villi and intervillous space.

Case 3

This 23-year-old primipara booked for her confinement at 22 weeks, on 4 January 1965, having then a blood pressure of 125/80 mm.Hg. On 2 March her blood pressure was found to be 150/110 mm.Hg and she developed a persistent albuminuria of + to ++. The blood urea was 17 mg./100 ml. and her urine was concentrated to 1,016 and diluted to 1,006.

Foetal growth was markedly retarded and on 23 April an elective caesarean section was performed owing to further clinical deterioration.

A female baby was born weighing 3 lb. 10 oz., with an Apgar rating of 10/10. The placenta weighed 13 oz. and one-third was occupied by white infarcts, as assessed macroscopically and microscopically.

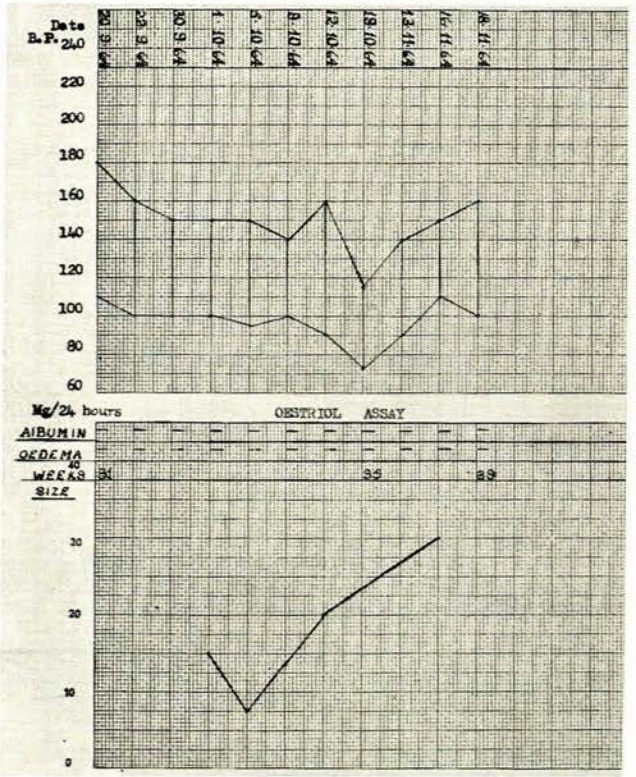

Fig. 2. See text.

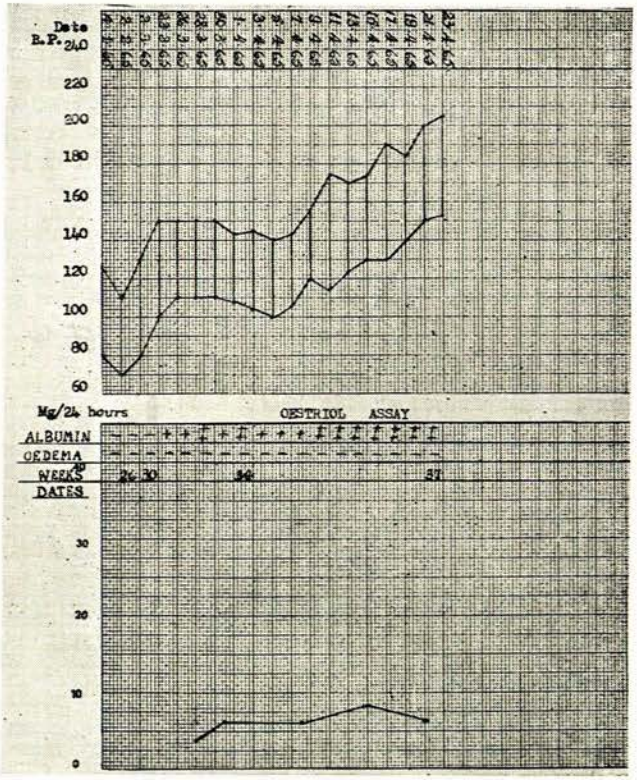

Fig. 3. See text

Interpretation. The clinical picture of this patient left little doubt that there was placental insufficiency and intra-uterine growth retardation. Oestriol figures confirmed this view (Fig. 3). Though the last oestriol assay was done 2 days before termination, this did not reflect any marked deterioration which would have indicated the urgent necessity for termination.

From the clinical assessment it was thought that little was to be gained by waiting longer and that sudden intra-uterine death was a distinct possibility, a view which was amplified by the placental findings.

Case 4

The patient was a 25-year-old primipara, who was referred to hospital on 22 November 1964 when 24 weeks pregnant, having a blood pressure of 120/70 mm.Hg and marked albuminuria and oedema.

She was admitted to hospital, but despite continuous hospitalization her blood pressure started to rise. When rapid further deterioration occurred at 31 weeks, an induction was performed on clinical grounds.

The urine which was collected during the 24 hours of most rapid terminal deterioration, showed a marked rise in oestriol excretion. This result was obtained only after surgical induction and successful delivery of a male infant weighing 3 lb. 7 oz., with an Apgar rating of 4/10.

The placenta weighed 8 oz. and a quarter was occupied by white infarcts and one red infarct pattern A.[10] Histologically the decidual spiral arterioles showed extensive fibrinoid necrosis and thrombosis and the white infarcts were confirmed.

Interpretation. Rapid clinical deterioration at 31 weeks in a fully hospitalized patient dictated termination at this time. The placental findings confirmed that this line of management was correct.

In spite of the fact that the last oestriol was collected during this phase of rapid deterioration, it did not reflect such a state (Fig. 4). If the result had been obtained within hours of collection and found to have been 18·5 mg./24 hours, definitive management may have been delayed. Considering the rapid deterioration and degree of placental damage, such would have been misguided delay.

It thus appears that a more rapid oestriol assay service might have resulted in a stillbirth if the clinician had been influenced by the result obtained.

Case 5

This 30-year-old gravida 4 had 3 live children of about 8 lb. each. She was first seen on 29 June 1964 at 20 weeks presenting with a blood pressure of 130/70 mm.Hg and albuminuria +. When the slight albuminuria and oedema was followed by a rise to 140/90 mm.Hg in blood pressure, she was admitted to hospital on 22 October for full investigation and was found to have systemic lupus erythematosus. Oestriol excretion remained satisfactory. When a drop in oestriol excretion occurred from 21 to 26 November, and this was followed by a more rapid rise in blood pressure, it was regarded that the time had arrived for termination. Induction produced a healthy male infant weighing 6 lb. 10 oz. with an Apgar rating of 6/10. The last urine which was collected during the 24 hours just before delivery, did not confirm a falling oestriol level. The placenta, weighing 13 oz., was normal macroscopically and microscopically.

Interpretation. We know that albuminuria, unassociated with hypertension, on the whole carries a different foetal prognosis than when the blood pressure is raised. Thus when hypertension became superimposed on albuminuria + + +* and oedema, and the foetus weighed at least 5½ lb., induction was carried out. The falling oestriol seemed to confirm the wisdom of this line of action.

However, when the last oestriol result became available after induction (Fig. 5), the anticipated further drop had not occurred. This stresses the point that at least 3 successive readings should confirm a falling oestriol excretion before it can be used as indicative of a trend.

*Persistent albuminuria heralds a poor prognosis for both mother and foetus when systemic lupus erythematosus is the aetiological factor.[13]

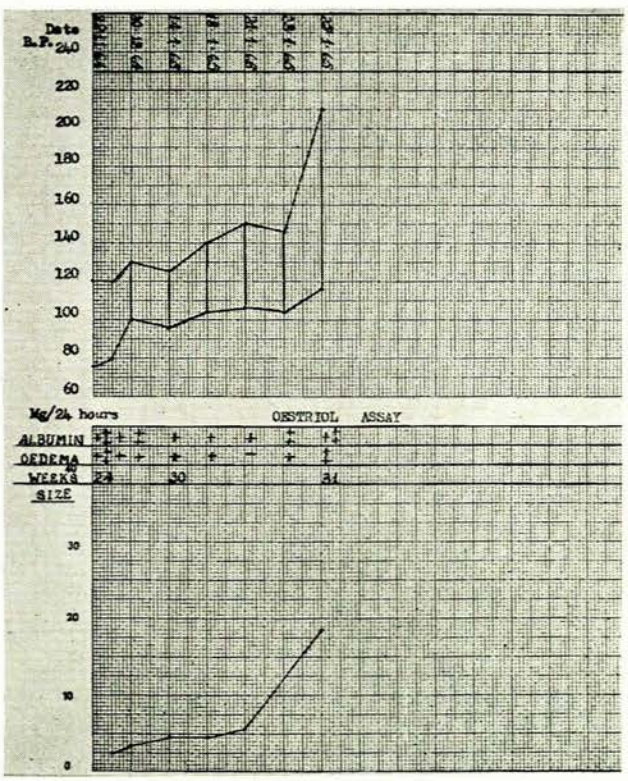

Fig. 4. See text.

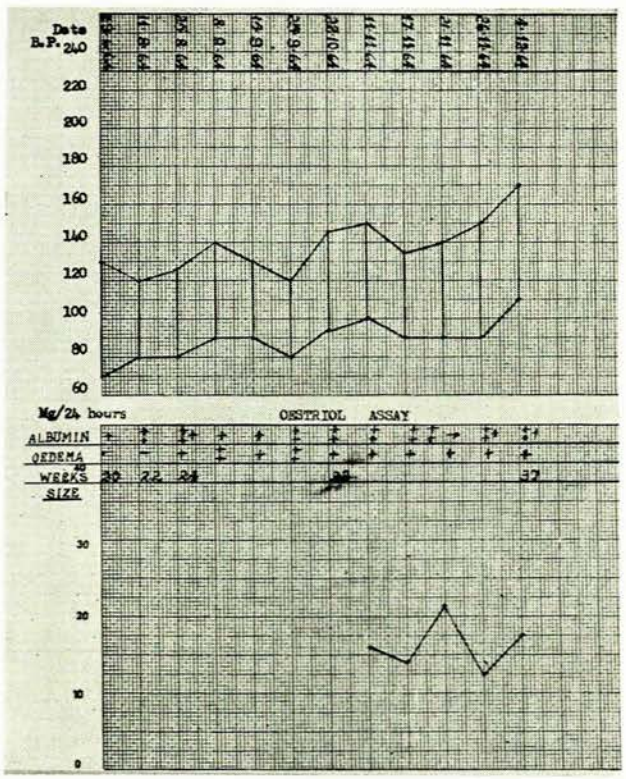

Fig. 5. See text.

The oestriol assay thus did not really help in determining the outcome here, and if it did, it was in a fortuitous way.

Case 6

This patient was a 24-year-old gravida 5, para 2. She was first seen at 28 weeks on 4 January 1965, having a blood pressure of 180/110 mm.Hg. Three weeks later her blood pressure had risen to 200/130 mm.Hg.

On bed rest in hospital the blood pressure gradually dropped to 130/70 mm.Hg and on 1 March she was inadvertently allowed to go home.

The oestriol excretion ran a fluctuating course, but from 15 February appeared to be dropping persistently.

She returned for the first time on 16 March 1965, with a blood pressure of 200/130 mm.Hg and she was assessed to be 38 weeks pregnant. Successful immediate induction was followed by an instrumental delivery of a male infant weighing 6 lb. 3 oz. with Apgar 10/10. The normal-looking placenta weighed 16 oz. and at histological examination the spiral arterioles, decidua and villi were essentially normal.

Interpretation. Prolonged hospital confinement had resulted in such satisfactory progress with regard to blood pressure and foetal growth, that she was eventually allowed to go home in spite of the relatively poor prognosis at 30 weeks with a blood pressure of 200/130 mm.Hg.

The oestriol figures may be viewed from two aspects (Fig. 6), namely the interpretation of fluctuation and of successively falling excretions.

If there is a spontaneous fluctuation between $7\frac{1}{2}$ - $22\frac{1}{2}$ mg./24 hours during the course of a few days when clinical progress is satisfactory, what could be the value of fluctuations at low levels? Surely in the same way in which there may fortuitously be 3 successive reducing readings at high levels, this may also occur at low levels and thus create the wrong impression of imminent catastrophe—in other words, the readings of the individual case may be extremely difficult to interpret in clinical terms.

In spite of all the oestriol assays in this patient, in whom it was thought that they would certainly be of value, the eventual decision to carry out the termination was done on clinical grounds entirely. The oestriol values thus ultimately played no role in the management.

Case 7

This 30-year-old primipara was first examined when 26 weeks pregnant on 21 December 1964. She then showed a blood pressure of 135/90 mm.Hg and appeared clinically to fall in the dystocia-dystrophia group. In addition the haemoglobin was 9 G/100 ml. and her Wassermann test was positive.

Though the highest blood pressure was 150/100 mm.Hg, and most of the time much lower, it was thought advisable to keep her in hospital because of the general clinical circumstances, the poor foetal growth rate and persistently low oestriol excretion. The last oestriol urine was collected when further fairly rapid clinical deterioration occurred with a rise of blood pressure to 180/110 mm.Hg and albuminuria + +.

Avertin was administered and a pitocin drip commenced as the first phase of the induction of labour.

The foetal heart rate increased to 180/min. and a caesarean section was performed. A live male infant weighing 3 lb. 5 oz. with Apgar 6/10 was born. The placenta of $7\frac{1}{2}$ oz. had a number of thrombosed spiral arterioles on the decidual surface and 6 white intraplacental infarcts. These features were confirmed histologically.

Interpretation. The low oestriol results (Fig. 7) tended to confirm the clinical impression that this pregnancy was endangered. The low figures of 3 - 4 mg. were followed by a further week's survival *in utero* when the figure dropped to 0·8 mg. in 24 hours. In spite of this extremely low figure, the foetus survived. This result became available only after delivery, the ultimate practical management of the case having been dictated by the blood pressure, albuminuria and foetal heart rate.

The oestriols, therefore, correctly forecast placental insufficiency and intra-uterine foetal growth retardation, but failed

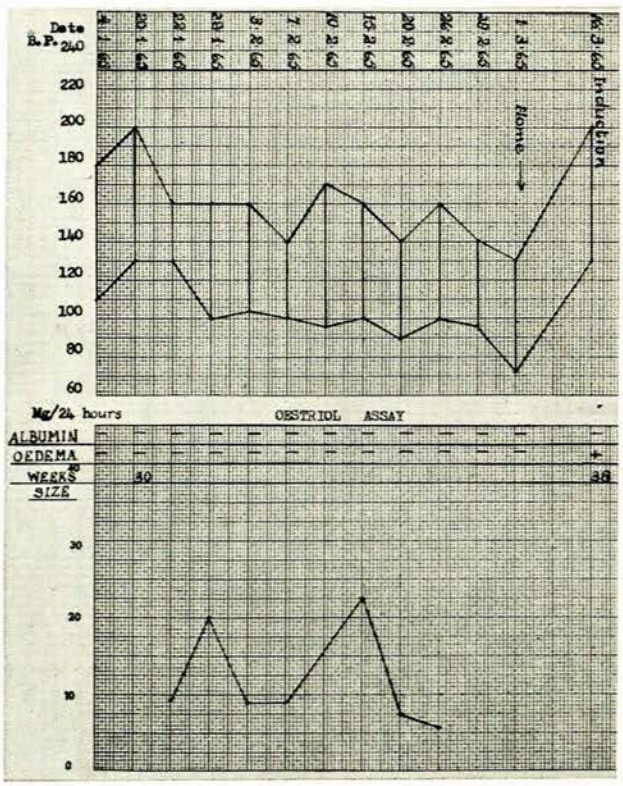

Fig. 6. See text.

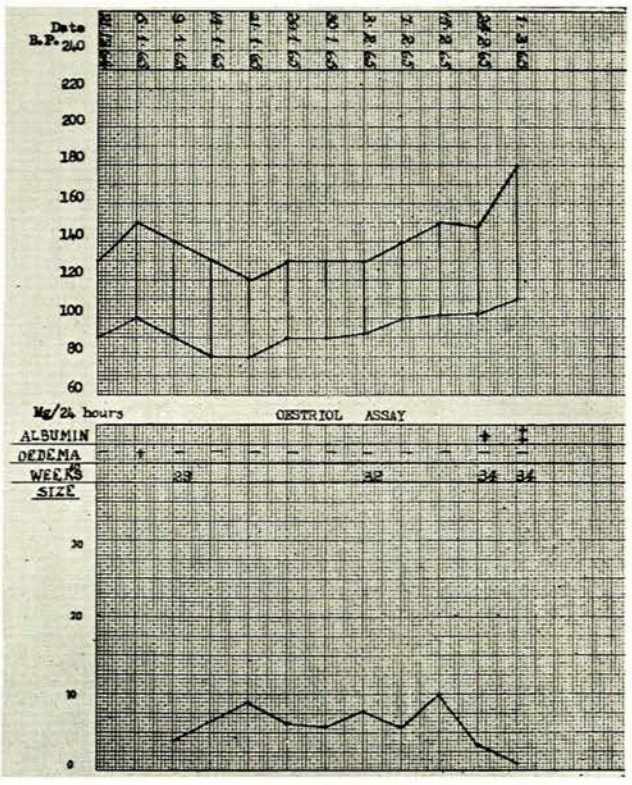

Fig. 7. See text.

to do so more accurately than clinical assessment, nor did they finally dictate the end point.

Case 8

The first pregnancy of this healthy 33-year-old gravida 3, para 2, ended in an unexplained stillbirth of a baby weighing 6 lb. 2 oz. The 2nd child was born alive. It weighed 7 lb. 2 oz. and died of an undefined cause at the age of 2 months. All investigations to try and establish a cause of the antecedent foetal loss, were uninformative. The highest recorded blood pressure was 140/100 mm.Hg.

An oestriol assessment was done to determine whether placental insufficiency was present, this not being evident on clinical

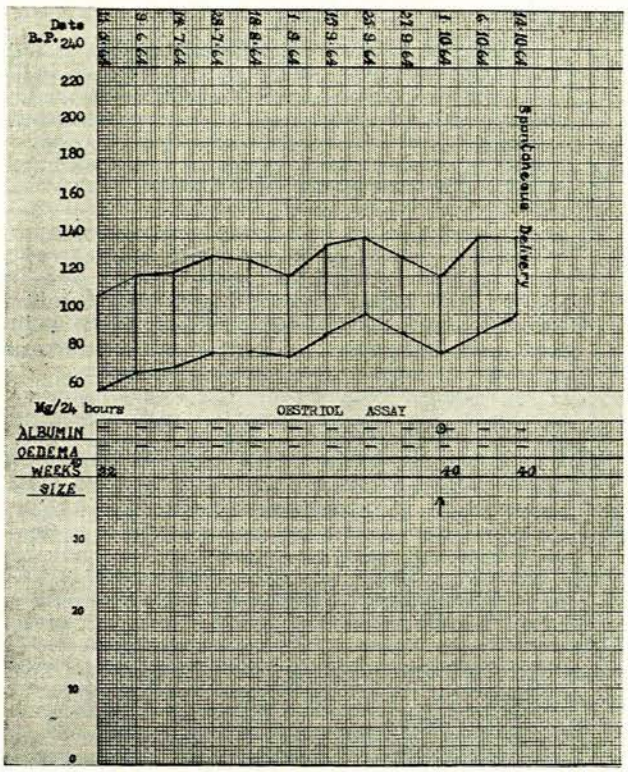

Fig. 8. See text.

grounds. When the very high figure of 48·5 mg. per 24 hours was obtained (Fig. 8), it was not thought necessary to repeat it. She came into spontaneous labour and delivered a male infant of 6 lb. 8 oz. normally after a total labour of 4½ hours. All efforts to resuscitate the baby failed. It appeared normal. A postmortem examination was not done. The placenta weighed 20 oz. and its macroscopic and microscopic features showed no detectable abnormalities.

Interpretation. The cause of death remained unexplained. Clinically the pregnancy advanced satisfactorily and the single oestriol reading near delivery, confirmed this. The oestriol thus failed to sound the warning note where placental insufficiency was not suspected on clinical grounds. Because the baby was thought to weigh about 5½ lb. on 1 October, which was the patient's due date, it was assumed that she was out by a month with her dates. She was therefore not induced at this stage. This approach was confirmed by the high oestriol figure.

CONCLUSIONS

Those patients who showed persistent low oestriol excretion figures, all had overt clinical evidence that placental insufficiency existed and that foetal life was endangered. The over-all validity of the excretion levels which Banerjea[1] gave for 215 cases, was confirmed.

In none of the cases in this series were the oestriol figures indicative of imminent foetal death, without there having been fairly rapid clinical deterioration which dictated immediate definitive therapy. In these cases confirmatory spiral arteriolar and placental evidence was almost always present indicating that clinical and oestriol assessment were indeed correct.

Failure of oestriol assay to direct suspicion of placental insufficiency to the patient with the unexplained stillbirths, emphasize that low figures only tend to occur when there is already marked impairment of placento-foetal functions, due mainly to the presence of the renal-hypertensive group of pregnancy disorders.

Since the oestriols may fluctuate so much from day to day, they will have to be assessed and the results made available on a daily basis during the final phases of such a pregnancy. At least 3 successive reducing levels should be obtained before this can be accepted as a trend.

When it is considered that a live child was obtained in the present series with an oestriol excretion reading of 0·8 mg. in 24 hours on the day preceding delivery, it is clear that this test may be used only as corroborative evidence that the optimum time for delivery had been reached, but that it is rarely low enough to be indicative of imminent foetal death, if clinical evidence is not already indicating such.

It thus appears that the oestriol assay will mainly be of value if employed as corroborative evidence of placental insufficiency in, for instance, patients with poor obstetric history due to the renal-hypertensive group of pregnancy disorders or primiparae aged 30 years and older in this group.

In general Banerjea,[1] Martin and Hahnel,[11] Wray and Russell[14] and Booth *et al.*[2] had come to similar conclusions.

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We are also greatly indebted to the many members of the medical and nursing staff of the maternity hospitals under the auspices of the University of Cape Town, who made the study possible.

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