Monitoring the fetoplacental unit—the fetus

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Summary

Information concerning the value of steroid assays in monitoring the fetoplacental unit is reviewed. The emphasis is placed on urine and plasma oestriol concentrations, their relationships to one another and to abnormal gestation.

RECENT textbooks of obstetrics show that a great array of techniques have been proposed for measuring the well-being of the fetus *in utero*. Few of these have spread beyond the zone of operations of their optimistic progenitors and even less qualify for the designation of recent advances. In order to reduce the field to manageable proportions, only one technique of fetal monitoring, that of hormone assay, will be considered. In this context one hormone in particular has captured attention. This is the oestrogen metabolite, oestriol. Much of the interest in this compound derives from the fact that the fetal adrenal and liver as well as the placenta are concerned in its biogenesis. Indeed, the very raw material from which oestriol is made—dehydroepiandrosterone—is produced by the fetal adrenal, and the insertion of the characteristic hydroxyl group at C16 is done by fetal liver enzymes. The levels of oestriol in the maternal organism may, therefore, be presumed to reflect the fetal state as much as placental function.

For a good many years estimations of urinary oestriol output have been a favoured method of assessing fetal well-being. This method has been so widely used that a small river of urine has come to run from most maternity units in this country. As more and more estimations came to be done, the process was automated and many institutions have acquired expensive gadgets to cope with the problem. What are we getting for our money?

Greengrocers selling apples tend to display the most attractive fruit in the front of the tray. The first few figures are intended to do the same for urinary oestriol measurements by illustrating the most favourable results of the assay. Because of the fetal element in its biogenesis, oestriol excretion is most directly affected in conditions of primary fetal rather than placental pathology, such as retarded fetal

growth. Figure 1 shows a group of oestriol excretion values in urinary collections made a few days before the mother gave birth to a growth-retarded fetus.

FIG. 1. Oestriol excretion in severely retarded fetal growth. x, subsequent fetal death; o, fetus survived.

It is evident that not only does oestriol output tend to be low in fetal growth retardation but also that the values are lowest in those cases having the worst prognosis, i.e. when the pregnancy is going to end in perinatal death.

Cross-sectional data of this kind are useful for displaying the fact that there is a tendency for urinary oestriol to be low when fetal growth is retarded, but clearly there is so much overlap with the normal that such measurements are of no use as a means of diagnosing the condition. In practice, the real usefulness of the assay lies in doing serial assays as a measure

FIG. 2. Oestriol excretion in retarded fetal growth compared with the normal levels.

of control, based on the assumption that oestriol output will decline *pari passu* with the deterioration in fetal condition. Most of the evidence which has been put forward in this respect is of anecdotal nature. It is easy enough to select a 'typical' case. 'Typical' implies the existence of criteria of type. Selection of typical cases without giving criteria of type is typical only of the prejudices of the observer. A description of the universe of oestriol excretion in retarded fetal growth is attempted in Fig. 2. It contrasts the mean and standard deviation of oestriol excretion week by week in a group of women who eventually gave birth to a growth-retarded child with the weekly values in a group carrying a normally grown child.

It can be seen that as pregnancy advances these two universes move further and further apart. In normal women a sharp increase in oestriol excretion occurs after 34 weeks; probably a new factor in oestriol biogenesis is engendered by the fetus (Kloppe and Billewicz, 1963). This new element in oestriol biogenesis appears to be lacking when fetal growth is retarded, so that the oestriol excretion is characterized by levelling off when it rises rapidly in normal pregnancy.

Urinary steroid assays have some major disadvantages as a measure of fetal well-being. The oestriol output, even in normal pregnancy, varies greatly from one day to the next. The shorter the time of urine collection, the more variable is the oestriol output.

The optimum period of collection is 48 hr and the minimum is 24 hr (Kloppe, Wilson and Cooke, 1969). It is therefore at least 24 hr after the decision to do the assay before the laboratory work can even be started. It then takes at least one more day before the measurements are completed. Obstetric diseases sometimes change rapidly and the results of oestriol assays may not become available until after the clinical decisions have been made. Between oestriol production in the fetoplacental unit and its excretion in the maternal urine, lie many steps such as metabolism by the maternal liver and handling of the steroid by the maternal kidneys. Each of these tend to impose their own effects on the oestriol levels in the maternal urine. In the end, urinary measurements show the fetoplacental unit only 'as through a glass darkly'. Measurements in blood, as opposed to urine, would take the assays one step nearer the fetoplacental unit and the long collection time would be cut out. For these reasons investigators have long hoped to measure oestriol in blood and many tentative methods have been published. In the end, these failed because of the tiny amounts of steroid involved. The oestriol content of a 24-hr urine is measured in milligrams, the oestriol concentration in blood requires the measurement of nanograms of material, a problem beyond the capacity of the most sensitive and specific chemical techniques which could be devised.

The scene has been wholly transformed by the introduction of radioimmunoassay. This technique has 'charmed magic casements opening on the foam of perilous seas, in faery lands forlorn'. It is the navigation of these perilous seas which I wish to examine.

Paradoxically, now that we have the tools for plasma steroid assays, we are beginning to realize some of the disadvantages of plasma assays. Urinary oestriol is the end of a metabolic process. Nothing more can happen to the steroid once it is in the urine. Plasma estimations are in the middle of a metabolic chain: an uneasy shifting balance point between inflow and outflow. A urine collection compresses the events of the previous 24 hr into a kind of summary, plasma measurements are a snapshot, a moment in time, reflecting only the conditions prevailing when the blood was drawn. The whole value of plasma oestriol assays is critically dependent on the variability of the steroid concentration from minute to minute and day to day. In urine almost all the oestriol is in one form, the C16 glucosiduronate. In blood there are four major oestriol components: unconjugated oestriol; oestriol-16-glucosiduronate; oestriol-3-sulphate; oestriol-3-sulphate-16-glucosiduronate. Which of these most nearly reflects the fetal state? Or is the total plasma oestriol the most faithful reflection of the amount of steroid being produced by the fetoplacental unit?

For technical reasons it is a good deal easier to measure unconjugated oestriol in plasma than it is to measure total plasma oestriol, and most of the assays which are now being set up in various parts of the world have concentrated on the measurement of the unconjugated steroid. Before deciding the value of plasma oestriol assays it seemed important to get data on the day-to-day variability of both total and unconjugated plasma oestriol. This study was done on ten primigravid volunteers, all thirty-eight weeks pregnant. They were admitted to a metabolic research ward and continuous 24 hr urinary collections done for 6 days. Each morning at 9 a.m. before breakfast, a specimen of blood was taken from each volunteer. The mean values of total plasma oestriol are shown in Table 1.

TABLE 1. Day-to-day variation of total plasma oestriol in pregnancy (6 days, ten patients)

Group mean value	16.3 $\mu\text{g}/100\text{ ml}$
Average standard deviation	1.8 $\mu\text{g}/100\text{ ml}$
Average coefficient of variation	13.2%

It is evident from Table 1 that the total plasma oestriol is very steady from day to day, and that a significant change in the trend would be easy to detect. How does this compare with other parameters such as unconjugated oestriol or urinary oestriol output?

The results of these measurements are shown in Table 2.

TABLE 2. Day-to-day variation in oestriol levels (6 days, ten patients)

Parameter	Average coefficient of variation (%)
24-hr urinary oestriol excretion	21.3
Total plasma oestriol	13.2
Unconjugated plasma oestriol	30.9

It would appear that, at least from the point of view of variability, total plasma oestriol is the measurement of choice. It is less variable than the urinary oestriol output in the same patients.

The steadiness over time of total plasma oestriol concentration does not establish the usefulness of the assay of this steroid in the assessment of fetal well-being. It must be shown that in a particular category of obstetric disease the oestriol concentration changes rapidly and markedly in keeping with the severity of the condition. Such a demonstration requires many assays in a variety of obstetric diseases and will not be made for some time yet. In the meantime the preliminary findings are encouraging. Some such findings were recorded by Masson (1973) and are shown in Fig. 3.

FIG. 3. Plasma oestriol concentration in normal pregnancy and in pre-eclampsia (from Masson, 1973).

This figure contrasts the universe of plasma oestriol in normal pregnancy with that obtaining in severe pre-eclampsia. The order of difference between the two is at least as great as that found for urinary oestriol in the case of retarded fetal growth.

FIG. 4. Correlation between urinary oestriol excretion and plasma oestriol concentration. $\tau = 0.68$, $\eta = 18$.

There is general agreement that in a number of obstetric diseases the urinary oestriol output reflects the fetal state. If, therefore, plasma oestriol concentration correlates with urinary oestriol output in such diseases it is likely that the plasma levels will bear a

similar relationship to the fetal state. The correlation between urinary oestriol output and plasma oestriol concentration in the same patients is shown in Fig. 4.

Those of us who have devoted much time to the elaboration of methods for measuring plasma oestriol are in danger of being carried away by our enthusiasm. We tend to think of plasma measurement as a sophisticated version of the urinary assay. It is nothing of the sort. Plasma measurements are to be regarded as a different concept. They are not a simple reflection of fetoplacental production of oestriol. They are the outcome of three variables: rate of production; the size of the maternal pool into which the oestriol flows; the rate at which it flows out of that pool. It needs a great deal more critical examination of these variables before any final verdict on the usefulness of plasma oestriol assays can be pronounced.

The assessment of fetal well-being has been the subject of many reviews. A critical examination of the various techniques was published by Klover (1970a) and hormone assays only were reviewed by Klover (1970b).

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