when daily estriol values indicated that intrauterine fetal death was not imminent.

It would seem, from the accumulated clinical and laboratory work done to date, that the urinary estriol excretion will assume a valuable place in the management of pregnancies commonly associated with a high perinatal mortality. The mechanism of production and metabolism of this estriol is not firmly established. Diczfalusy summarizes the present knowledge of the endocrine function of the placenta and concludes that the markedly increased amounts of estrogen excreted by the mother are produced by the placenta, probably by syncytial elements (Acta Endocrinol., *129:* Suppl. 50, 1960). The function of this estrogen is rather obscure but these compounds are probably essential for stimulating uterine growth. The fact that the placenta produces estrogen is indeed suggested by the presence of large amounts of this material when placental tissue is extracted. However, the theory of production of estrogen by the placenta is not unanimously accepted.

(See editorial note appended to next abstract.—Ed.)

URINARY ESTRIOL AS AN INDEX OF PLACENTAL FUNCTION. A STUDY OF 279 CASES

JOHN W. GREENE, JR., AND JOSEPH C. TOUCHSTONE

Department of Obstetrics and Gynecology, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

Am. J. Obst. & Gynec., *85:* 1, 1963

An intensive study using a chemical method for determining urinary estriol excretion and assessing placental function in normal and complicated pregnancy has been carried out. A total of 2,015 determinations have been completed during 279 pregnancies. Twenty-nine normal pregnancies have been followed from the eighth week until term. At least two determinations were done with each patient and 12 were followed with weekly determinations during the two months preceding delivery. The following abnormal pregnancies have been studied: 35 diabetic, 32 hypertensive and/or toxemic, 14 postdate, 26 instances of questionable fetal viability, 6 cases of Rh sensitization, and 137 miscellaneous conditions such as abruptio placentae, history of previous stillbirth, and unexplained intrauterine fetal death.

Figure 1 illustrates the normal estriol values that have been established by the present method. A wide variation may occur in estriol excretion amounting to 50 or 60 per cent, in apparently normal gestation, when daily determinations are performed. Nevertheless, a lower limit in normal gestation has been established. During the final four weeks, no estriol value fell below 7.0 and only occasionally was it less than 12.0 mg. per 24 hours. In normal patients every value

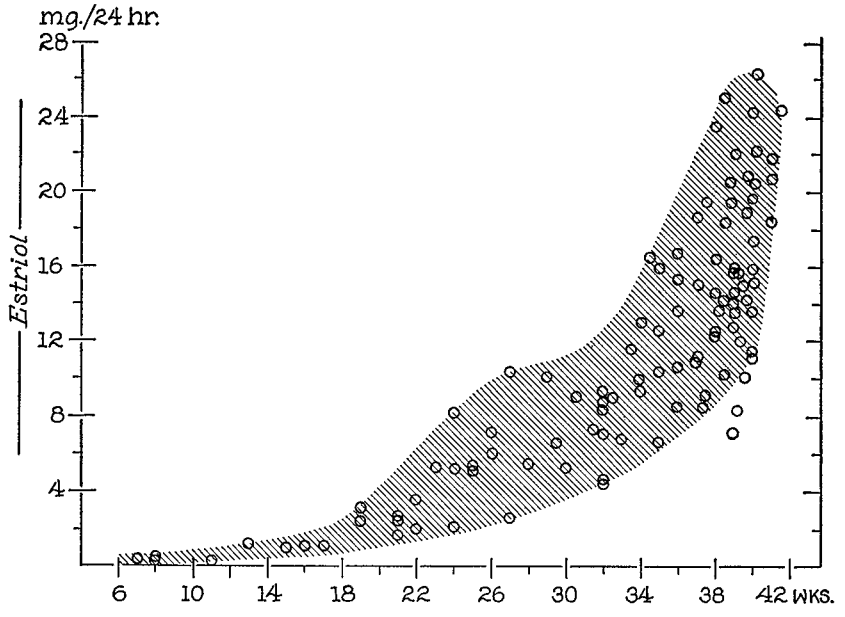

FIG. 1. Estriol values found in 29 uncomplicated pregnancies.

below 10.0 mg. per day returned to the usual range of 12.0 to 22.0 mg. within a day.

In 17 instances of clinically established intrauterine fetal deaths, it was certain the fetus had been dead at least 48 hours. Except for two instances of erythroblastosis, the estriol excretion was less than 1.0 mg. per 24 hours in every determination.

Sixteen instances of intrauterine fetal death occurred during observation. These pregnancies were complicated by diabetes, toxemia or hypertension. In each patient the clinician was certain the fetus was alive when the first determination was made because of the presence of fetal heart tones and fetal movement. All were delivered vaginally. The estriol levels appear in Figure 2. One patient had an estriol level of 6.2 mg. per 24 hours and one a value of 5.1 mg. per 24 hours before labor ensued. These infants died during labor. The others died before labor when values fell below 4.0 mg. The majority of intrauterine deaths occurred when values fell to 2.0 mg. or less.

Eight patients in whom the estriol excretion was abnormally low before the birth of an infant died in the neonatal period. Two of these infants had multiple congenital anomalies including coarctation of the aorta. The others were: one case of severe toxemia, one of diabetes and four of abruptio placentae.

Twelve complicated pregnancies in which estriol determinations indicated fetal jeopardy were terminated by cesarean section on the basis of an initial low value, a subsequent marked drop from a normal level, or as in one postdate pregnancy when a marked fall in titer occurred during false labor. Of 12 infants there were two neonatal deaths, both of apparently normal infants weighing

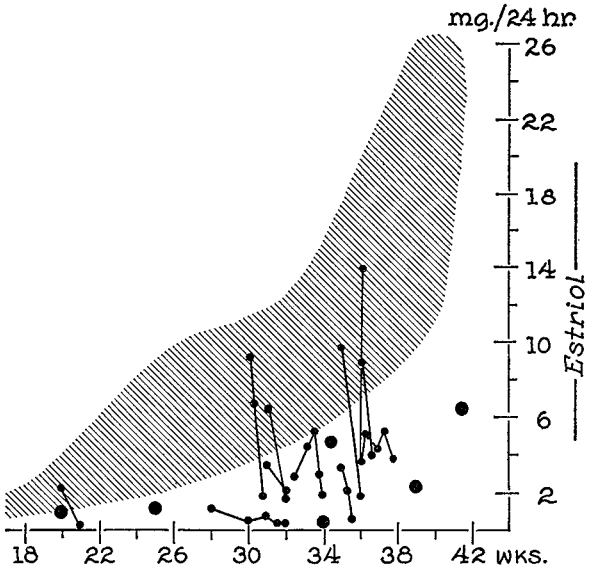

FIG. 2. Observation of fall in estriol excretion with intrauterine fetal death in 16 pregnancies. Fetal heart tones and movements were observed when first estriol determinations were made. All infants were delivered vaginally and were stillborn. Large dots represent single determinations. Shaded area is normal range taken from Fig. 1.

2,325 Gm. and 2,180 Gm. that died of pulmonary hyaline membrane disease 3½ and 4½ days after birth.

Thirty-five diabetic pregnancies have been studied in detail. Nineteen presented normal urinary estriol excretion throughout gestation and there was no perinatal difficulty. Sixteen patients presented problems in management. Four of these had initial values of less than 2.0 mg. and the infants died. The remaining presented terminal estriol values between 4.0 and 12.0 mg., but by means of cesarean section or timely delivery by induction the infants survived. Because of rapidly falling estriol values certain patients were subjected to cesarean section earlier than seemed clinically advisable. These babies survived. No fetal death occurred when the value exceeded 4.0 mg./24 hours.

Thirty-two cases of hypertension and/or toxemia were studied. When values fell below 4.0 mg. per day fetal death was predicted. This occurred in 9 of 13 births preceded by estriol output of 4.0 mg. per day or less. The remaining 4 of these 13 with low values were treated by prompt cesarean section and yielded living babies. Eleven values lay between 4.0 and 12.0 mg. with one perinatal death. An infant weighing 1800 Gm. died during labor when a value of 5.1 mg. was obtained prior to labor. In this group five cesarean sections and two inductions were done because values abnormal for the period of gestation indicated prompt delivery. These infants did well as did three that were delivered by spontaneous labor with values above 10 mg. There was no difficulty with those patients that presented values over 12 mg.

Estriol determinations were performed upon 26 specimens in which the ques-

tion of fetal viability arose during the second to sixth months of gestation. In 18 patients normal values were found for that period and healthy infants were delivered in each instance. In eight no estriol was detectable; six were delivered of macerated fetuses and two had hydatidiform moles which gave positive tests for chorionic gonadotrophin.

It was found that in Rh-sensitized parturients estriol excretion was not related to perinatal mortality except when intrauterine death occurred. Of six patients, two had normal values but the infants had severe erythroblastosis at birth and died. One patient excreted between 29.0 and 40.0 mg. per day and when the baby was delivered six exchange transfusions were necessary. This baby survived. Three patients had estriol values between 1.2 and 2.5 mg. per 24 hours after intrauterine death occurred.

(These two articles set forth, the first in a general way and the second in more detail, the extensive and valuable work of the authors on estrogen excretion as an index of placental function. The first paper, as originally published, contains also a rather extensive review of the literature.

It is generally recognized that a dependable test of placental function is one of the most urgent needs in obstetrics. As a consequence, numerous procedures for this purpose have been suggested. These fall into four main categories. (1) Maternal plasma or urinary concentrations of estrogen, progesterone (pregnanediol) or chorionic gonadotrophin, it being hypothesized—rightly or wrongly—that hormonal function parallels the function of the placenta as an organ of transfer. (2) Clearance time of radioactive substances, such as sodium, when injected into the myometrium. This is an indirect approach to the problem based on the assumption that the disappearance rate of radioactive sodium from the myometrium is an index of uterine circulation and therefore an indirect evidence of placental function. (3) The ability of the placenta to transfer from mother to fetus certain substances whose presence in the latter can be easily demonstrated. An example is the atropine test being studied by Hellman. (4) Electronic recordings of the fetal heart rate and electrocardiographic pattern. Only recently has it been possible to secure a clear-cut electrocardiogram of the fetal heart. This has at last been accomplished by Hon by means of a computer—work that will be published shortly. I have seen one of these tracings, which apparently can be reduplicated at will, and it was really beautiful, the pattern being just as clearly delineated as in the best adult electrocardiogram. Fetal bradycardia has of course long been recognized as one of the standard indices of acute fetal distress; but it is not necessarily a sign of placental insufficiency since it is often produced in other ways, as by prolapse of the cord or abruptio, for instance. Whether studies of the electrocardiographic pattern in cases of known placental insufficiency will show significant alterations, remains to be seen; but I should think that the odds are against it because in adults the electrocardiogram may be normal in the presence of profound hypoxia and even at the moment of death.

A number of authors have reported favorably on urinary estrogen levels as an index of placental function. Thus, Zondek and Goldberg have found them helpful in the latter half of pregnancy (J. Obst. & Gynaec. Brit. Emp., *64:* 1, 1957). In this country, E. Stewart Taylor, Bruns and their associates in Denver have done especially noteworthy work in this field (Am. J. Obst. & Gynec., *76:* 983, 1958; see also next abstract). They found that a persistently low level of urinary estrogens was suggestive of uteroplacental dysfunction in 74 per cent of the patients in which it was found. But in the remaining 26 per cent the pregnancy followed a normal course. Approximately the same figures obtained when the uterine clearance time of radioactive sodium was prolonged. Hence the authors conclude that "a low level of estrogen cannot be interpreted as significant if the pregnancy is progressing normally." But, in the presence of a toxemia, they say that they would attach

some significance to such a finding. From a practical viewpoint this is all-important since it is in patients with toxemia that we are especially concerned about the possibility of fetal exitus. Incidentally, Taylor and his group found that urinary pregnanediol levels were of no value as an index of placental function.

The value of the articles by Greene and his associates, abstracted above, lies not only in the large number of observations reported, but also in the fact that the authors cite specific concentrations of urinary estriol below which fetal death is very likely to occur. This figure appears to be 4 mg. of estriol per 24 hours. The data on the 35 diabetic gravidas are especially informative since here is another condition in which we have no reliable index of impending fetal death. If I interpret the authors' figures correctly, it would be wise to carry out immediate delivery, probably by cesarean section, if the urinary estriol falls below 10 mg. per 24 hours during the last month of a diabetic pregnancy. The same admonition would seem to apply during the last six weeks of a pregnancy complicated by toxemia.

If these prognostic relationships are valid, we have here a useful clinical guide. But, is the chemical work just too onerous to be practical? In certain Danish hospitals, all diabetic gravidas are hospitalized during the last six weeks of pregnancy and the blood sugar analyzed by a micromethod *four times daily* and the insulin requirements based on these determinations. By this means they have been able to achieve one of the lowest perinatal mortality rates in diabetes on record. Greene states that the chemical procedure they use for the determination of urinary estriol (always done in duplicate) can be completed in four to six hours. If the prognostic value of these analyses are as great as the authors' experience would indicate, the estimation of urinary estriol every day, or every other day, during the last six weeks of pregnancies complicated by diabetes or toxemia would not seem to entail a disproportionately large amount of work.—Ed.)

URINARY ESTRIOL EXCRETION OF PREGNANT PATIENTS WITH PYELONEPHRITIS AND RH ISOIMMUNIZATION

E. Stewart Taylor, Alfred Hassner, Paul D. Bruns and Vera Drose

Department of Obstetrics and Gynecology, University of Colorado, Denver, Colorado

Am. J. Obst. & Gynec., *85:* 10, 1963

This report deals with the measurement of urinary estriol levels in six pregnant patients with pyelonephritis and nine patients who were Rh negative and sensitized. Pregnant mothers with acute urinary tract infections were found to have a reduction in urinary estriol values. High levels of estriol were present in the urine of Rh-negative patients whose pregnancies resulted in the birth of an infant with erythroblastosis.

By addition of glucose before hydrolysis to normal pregnancy urine or to nonpregnancy urine to which 20 μg of estriol had been added, there was a chemical effect, though not very marked. The addition of 10 per cent sugar, a value considered high for diabetic urine, caused a decrease by 12 to 16 per cent in estriol values. This is not large considering that day to day fluctuations in estriol value in the average patient are of the same order. It suggests, however, that urinary sugar tests may be useful as an adjunct to estrogen determinations in the urine. The exact nature of the interaction caused by glucose is not known. These ex-