Yale University
EliScholar – A Digital Platform for Scholarly Publishing at Yale

Yale Medicine Thesis Digital Library | School of Medicine

1972

Child development after pregnancies complicated by low urinary estriols and pre-eclampsia

Michael W. Yogman
Yale University

Follow this and additional works at: http://elischolar.library.yale.edu/ymtdl

Recommended Citation
Yogman, Michael W., "Child development after pregnancies complicated by low urinary estriols and pre-eclampsia" (1972). *Yale Medicine Thesis Digital Library*. 3337.
http://elischolar.library.yale.edu/ymtdl/3337

This Open Access Thesis is brought to you for free and open access by the School of Medicine at EliScholar – A Digital Platform for Scholarly Publishing at Yale. It has been accepted for inclusion in Yale Medicine Thesis Digital Library by an authorized administrator of EliScholar – A Digital Platform for Scholarly Publishing at Yale. For more information, please contact elischolar@yale.edu.

T113
+Y12
3275

CHILD DEVELOPMENT AFTER PREGNANCIES COMPLICATED BY LOW URINARY ESTRIOLS AND PRE-ECLAMPSIA

MICHAEL WILLIAM YOGMAN

1972

MUDD
LIBRARY
Medical

YALE

MEDICAL LIBRARY

Permission for photocopying or microfilming of "Child Development After Pregnancies Complicated by Low Urinary Estriols and Preeclampsia"
(TITLE OF THESIS)

for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

Michael W. Yogman
Signature of Author

May 5, 1992
Date

CHILD DEVELOPMENT AFTER PREGNANCIES COMPLICATED BY LOW URINARY ESTRIOLS AND PRE-ECLAMPSIA

Michael William Yogman
B.A. Williams College, 1968

A Thesis Presented to the Faculty
of the School of Medicine, Yale University
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

Department of Obstetrics and Gynecology
Department of Pediatrics
Yale University School of Medicine

April, 1972

TO JUDY

Digitized by the Internet Archive
in 2017 with funding from
The National Endowment for the Humanities and the Arcadia Fund

https://archive.org/details/childdevelopment00yogm

Acknowledgements

I wish to express my appreciation to Dr. Leon Speroff and Dr. Nathan Kase of the Department of Obstetrics and Gynecology and to Dr. Peter Huttenlocher of the Departments of Pediatrics and Neurology at Yale University School of Medicine for their guidance throughout this research. I also with to thank the staff in Pediatric Clinic of Yale-New Haven Hospital for their help in enabling me to perform follow-up examinations on the children. Thanks also go to Miss Dawn Sassi and Mrs. Nancy Holt for technical assistance. Most of all, I would like to thank the mothers and the children who all made a special trip to the clinic for this research study so that future mothers might deliver healthier babies.

ABSTRACT

A study of maternal estriol excretion and subsequent child development in twenty-one pregnancies is reported. Thirteen mothers had abnormally low estriol excretion patterns and six of their children were small for dates. On follow-up examination, five of these children had major problems in development or function, such as microcephaly,seizure disorder, and developmental retardation with hyperactivity. Defects were more related to chronically low estriols than precipitously dropping estriols. Eight mothers had normal estriol excretion with toxemia, and all eight children weighed more than 2500 grams, and were normal on follow-up.

Mothers with chronically low estriols tend to be older, to have more severe toxemia, and to give birth to more small-for-dates infants than mothers with normal or precipitously dropping estriols. These infants in turn are more likely to be abnormal.

Mothers with precipitously dropping estriols have milder toxemia and give birth to more normal weight infants who uniformly do well. If these infants are of appropriate gestational ages when the drop occurs, they should be delivered immediately.

The data also suggest that if during pregnancy estriols are chronically low, early delivery salvages many infants who later develop gross neurological and developmental defects. If such infants are not gaining weight in utero, perhaps some method can be found such as intra-amniotic alimentation to treat the growth retardation.

TABLE OF CONTENTS

I. INTRODUCTION

Recent advances in prenatal care have enabled many women to deliver apparently healthy babies in spite of serious complications during their pregnancies. One of the most helpful techniques has been the monitoring of maternal 24-hour urinary estriol levels in an attempt to assess the health of the feto-placental unit. During the past ten years, obstetricians throughout the world have increasingly relied upon this test as a guide for intervention in complicated pregnancies. By indicating fetal distress, estriol excretion has in part been responsible for decreasing perinatal mortality rates.

In the past few years, physicians have begun to wonder if the infants salvaged from these complicated pregnancies would grow to be normal, healthy children and adults, particularly after Wallace and Michie (1966) found that 6 of 14 children whose mothers had low urinary estriols had developed neurological impairments by age two. Other investigators have published conflicting results. Green et al. (1969) studied 22 children whose mothers had low estriol excretion and found that at ages one to eight, one-third of these children had developmental delays, while in a control group of 12 children whose mothers had normal estriol excretion, one-quarter had developmental delays. They found no gross neurological defects in any of these children and no clear relationship of developmental delays to estriol excretion and concluded that abnormal estriol excretion during pregnancy was compatible with normal growth and development of children later in life. However, some mothers in their study had no underlying maternal disease, while others had diabetes, pre-eclampsia, or hypertension, and they did not account for the

influence of maternal disease on later child development. This uncontrolled variable of maternal disease in their study makes it almost impossible to relate later child development solely to estriol excretion pattern. The purpose of this study, therefore, was to follow up the growth and development of those children born at Yale-New Haven Medical Center whose mothers had low estriol excretion in the last trimester of pregnancy as well as the same maternal disease, pre-eclampsia.

A. Estriol Biosynthesis and Metabolism

The estriol that appears in maternal urine during late pregnancy is the result of contributions from both the placenta, and the fetal adrenal gland and liver. Because of enzyme deficiencies, the placenta alone does not produce estriol from cholesterol, progesterone, or even from the metabolism of estradiol, but rather must use precursors supplied mostly by the fetus (Hellman et al., 1971; Diczfalusy, 1964; Diczfalusy et al., 1965; Leffert, 1970). Dehydroepiandrosterone sulfate (DHAS) is the main precursor for estriol synthesis and is derived primarily from the fetal adrenal gland with a small contribution from the maternal adrenal gland (Klopper, 1968; Frandsen and Stakeman, 1961; Hausknecht, 1965; 1967). DHAS is then 16-hydroxylated by the fetal liver and sulfonated by several fetal tissues, primarily the liver. Finally, it is transferred to the placenta where it is hydrolyzed by sulfatases to the free compound 16α-OH DHA (Leffert, 1970; Diczfalusy, 1969). The main fetal contributions to estriol production are supplying adrenal precursors and liver enzymes for 16-hydroxylation. A failure of fetal activity at either point will cause a fall in maternal urinary estriol output (Klopper, 1968).

The conversion of 16α-OH DHA to estriol via 16α-OH androstenedione and 16α-OH estrone, takes place primarily in the placenta. Ryan demonstrated this conversion in vitro and found high concentrations of the enzymes that carry out aromatization of ring A of the steroid nucleus in the placenta (Sliteri and MacDonald, 1966; Ryan, 1962). Although this is quantitatively the most important pathway for estriol formation, placental estrone and estradiol also make small contributions to maternal urinary estriol excretion (Hellman et al., 1971). Free estriol formed in the placenta passes to the maternal blood to be reconjugated in the maternal liver with both sulfate and glucosiduronate and then excreted in the urine. Estriol conjugates constitute over 90% of the total estrogen excreted in the urine during late pregnancy, and therefore total estrogen levels in urine reflect estriol levels which monitor the adequacy of the feto-placental unit (Klopper, 1968; Greene et al., 1965). The pathways are outlined in the diagram on the next page (Figure I).

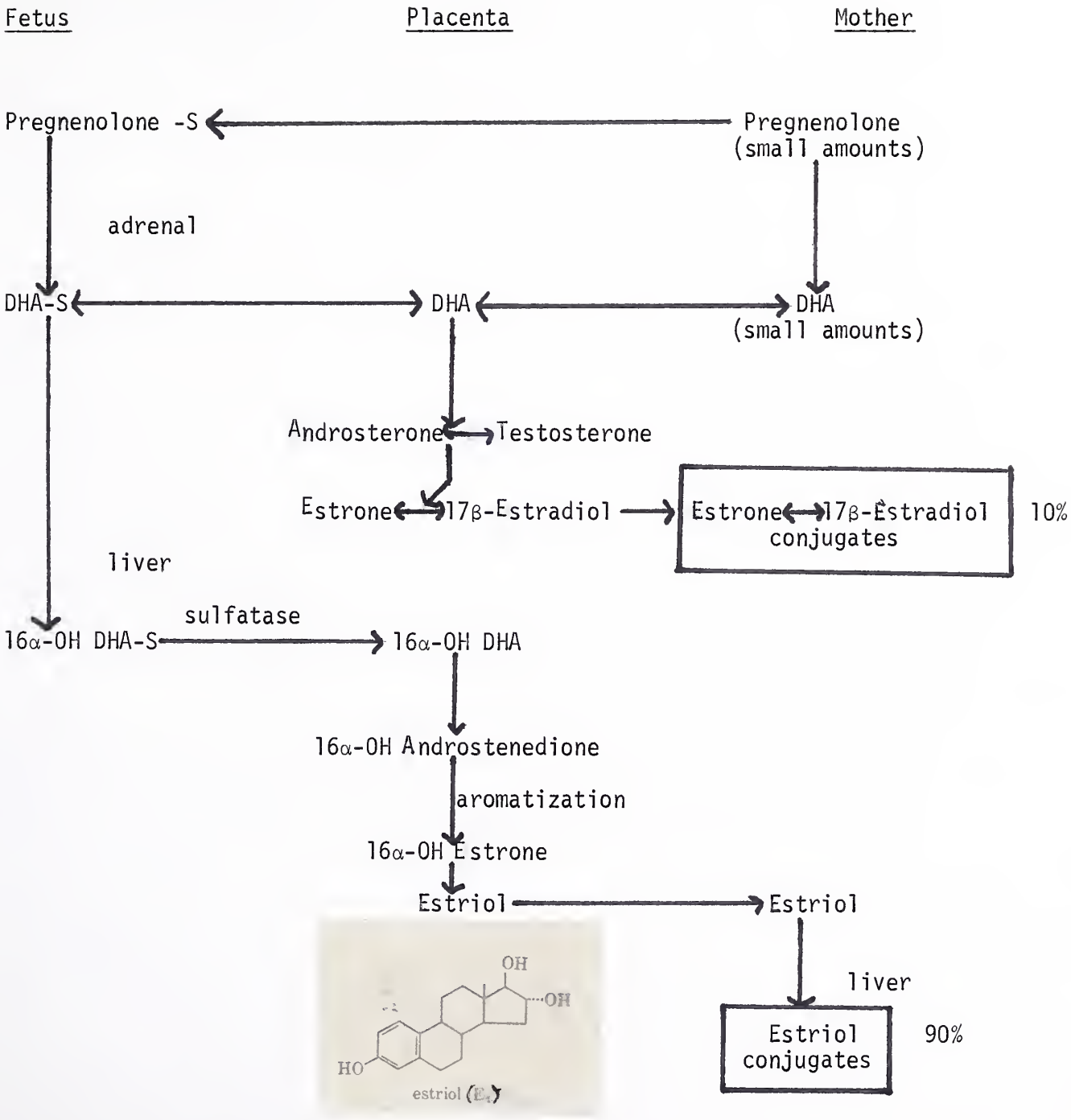

Figure I. Estriol biosynthesis and excretion during pregnancy.

B. Clinical Uses of Estriol in Pregnancy

The presence of estriol has been measured not only in maternal urine but also in maternal venous blood and amniotic fluid. Although measuring blood rather than urine levels would eliminate the variables of maternal hepatic and renal function, as well as the errors involved in 24-hour urine collections, the blood levels of normal pregnancies extend over a much wider range than urinary levels and are therefore less useful (Klopper, 1968; Roy et al., 1963). Normal amniotic fluid estriol values also have a wide range (Schindler and Hermann, 1966), but they do appear to be consistently low in the presence of severe fetal disease (Berman et al., 1968; Aleem et al, 1969). There is no evidence, however, that they reflect fetal status more accurately than urinary levels, and the simpler test is therefore the clinically accepted one at present.

In normal pregnancies, urinary estriol levels increase gradually until the thirty-second week and then more steeply, from a level of 0.1 mg. per 24 hours in the first trimester to levels of 20.0 to 50.0 mg. per 24 hours at term, varying with the method used (Greene et al., 1963). Variations in excretion exist both from patient to patient and from day to day in the same patient, and therefore, serial determinations are necessary. After the thirty-third to thirty-fourth week of pregnancy values below 4 mg. per 24 hours indicate impending or actual fetal death, while values from 4-12 mg. per 24 hours or drops of 60% or more indicate fetal jeopardy. Values above 12 mg. per 24 hours indicate healthy fetuses, except in pregnancies complicated by erythroblastosis (Greene and Beargie, 1970).

Estriol excretion has been studied in pregnancies complicated by intrauterine growth retardation, toxemia, diabetes mellitus, erythro-

blastosis and other problems. The relationship between low estriol excretion and intrauterine growth retardation (small-for-dates infants) appears to reflect, at least in part, the general relationship between estriol excretion and fetal weight. In normal pregnancies estriol excretion can be directly related to fetal weight. In 1963, Greene et al., found that in 31 normal pregnancies if estriol excretion was above 12 mg. per 24 hours, fetal weight would be 2500 gms. or more. Beling (1963; 1967) found a similar correlation— heavier babies giving rise to a larger estriol output. Exceptions do occur however. Klopper et al.in 1963 found that 3 of 37 otherwise normal pregnancies that resulted in small-for-dates infants had normal estriol levels, and similarly, Michie (1967) found that 7 of 16 surviving small-for-dates infants were the results of pregnancies where estriol excretion was normal one week before delivery. Nevertheless, when patterns of estriol excretion based on serial assays were used instead of single values, there was a correlation between the severity of the low maternal urinary estriol excretion pattern and the degree of low birth weight of the infant (Galbraith et al., 1970).

In pregnancies complicated by pre-eclampsia, a clear relationship appears between estriol excretion and birth weight. Both Beling (1967) and Taylor (1965a) found a correlation between low estriol excretion and low fetal weight in toxemic pregnancies. Yousem et al. (1966) found that in 12 pregnancies three toxemic mothers with estriols less than 8 mg. per 24 hours had babies weighing less than 1500 gms., while another three with estriols greater than 8 mg. per 24 hours had newborns weighing more than 1800 gms. The low estriols associated with low weight infants could not be explained by a mistake in dates by the mother and a short intra-

uterine gestation, for even if the duration of gestation was determined from the birth weight rather than from the mother's dates, the estriol excretion was still low. Yousem et al. therefore concluded that estriol excretion did reflect fetal weight. Similarly, Kellar et al. in 1959 found that the babies of all three pre-eclamptic mothers whose estriol excretion was less than 10 mg.daily after the thirty-eighth week were small for dates.

Both low urinary estriols and low birth weights are statistical concepts and are therefore difficult to apply to individual patients. It is clear from the work of Beischer et al. (1968), however, that mothers with less than average estriol excretion give birth to babies with lower birth weights and to more small-for-dates babies. They showed that in a population of 597 consecutive pregnancies birth weights averaged 3441 gms. when estriols were normal and 3134 gms.when estriols were low, while intrauterine growth retardation occurred in 3.1% when estriols were normal and 21.1% when they were low. One explanation for this relationship was offered by Naeye (cited in Wallace and Michie, 1966) who found that small-for-dates babies had reduced mass of the adrenal cortex; he equated the reduced mass with reduced function and decreased estrogen precursor production. Klopper (1968) concluded that although there is some overlap (approximately 10% of pregnancies with intrauterine growth retardation have had normal estriols), estriol excretion tends to be reduced when fetal growth is retarded. He felt that both the low estriol excretion and growth retardation are probably secondary to some form of feto-placental insufficiency.

Low estriol excretion has been found in pre-eclamptic pregnancies (Greene et al., 1963; 1965a; Taylor et al., 1965a), but the interpretation was complicated by the frequent simultaneous presence of intrauterine growth retardation and by the need for classifying pre-eclampsia both as to severity and duration. In mild pre-eclampsia, Klopper (1968) found average estriol excretion to be 85% of normal in patients with mild toxemia and felt that levels were markedly decreased only if the mild toxemia was longstanding. In a study of mild toxemics with low estriols, 3 of the 6 mothers gave birth to small-for-dates infants (Michie, 1967). Klopper found a mean excretion of 51% of normal and reported that 58% of the patients with severe toxemia studied by Lenters had low estriol excretions. Proteinuria in particular was associated with very low estriol excretion in severe pre-eclampsia (Michie, 1967; Taylor et al., 1965b). Wider fluctuations of estriol excretion occurred in toxemia than in normal pregnancy, but either low absolute values or consistent declines of 60-70% were signs of feto-placental insufficiency in pre-eclampsia as well as in other conditions (Greene et al., 1963). The influence of blood pressure alone on estriol levels in pre-eclampsia seemed minimal, since essential hypertension alone did not affect estriol excretion, and pre-eclampsia superimposed on hypertension affected estriols only in relation to the severity of the toxemia (Michie, 1967).

In pregnancies complicated by diabetes, urinary estriol excretion is usually within the high normal range,but dropping estriol levels indicate fetal jeopardy and are an indication for terminating the pregnancy after the thrity-fourth week (Taylor et al. 1965b; Greene et al., 1965b). In addition, estriol excretion appears to be related to the severity of the diabetes, lower levels occurring with more severe disease. The

incidence of low birth weight and malformed infants, however, was also higher in more severe disease (Beling, 1967). Serial assays were used to determine the time of delivery, but this technique did not appear to have decreased the perinatal mortality rate of 15% although prenatal deaths and stillbirths were decreased. (Greene et al., 1965b).

Urinary estriol excretion was not helpful in pregnancies complicated by Rh sensitivity, since many patients with erythroblastotic infants showed high urinary estriol excretion (Taylor et al., 1963). In addition, the low urinary estriol levels associated with impending fetal death in erythroblastosis did not occur far enough in advance to be helpful (Klopper, 1969). In summary, then, estriol excretion does reflect fetal weight, at least to some extent, and does reflect fetal distress and placental insufficiency in pregnancies complicated by pre-eclampsia or diabetes mellitus. For pregnancies complicated by Rh incompatibility, urinary estriol excretion does not accurately reflect the fetal condition.

C. Subsequent Development of Low Birth Weight Infants

Just as estriol excretion during various disorders of pregnancy is influenced by intrauterine growth retardation as well as maternal disease, any evaluation of child development must take into account the effects of birth weight on later development and the special characteristics of small-for-dates infants. In one study, the incidence of such small-for-dates infants (-2 S.D. below mean or less than third percentile) in pregnancies lasting at least thirty-three weeks was found to be 3% of surviving infants (Gruenwald, 1963).

Retrospective studies of childhood behavior disorders, mental deficiency, school performance, epilepsy, and cerebral palsy found an association between these defects and low birth weight (Eastman, 1962;

Lilienfeld et al., 1951; 1954; Pasamanick et al., 1956; 1960; Muller et al., 1971). As long as birth weights were controlled, socioeconomic factors did not appear to be involved (Knobloch et al., 1960). A prospective controlled study of the neuropsychiatric sequelae of low birth weight (<2500 gms.) compared 500 prematures with 492 term infants matched for race and socioeconomic status and showed an incidence of severe neurological defect of 8.2% in the low weight group versus only 1.6% in the control group at forty weeks of age. Over 25% of the prematures showed some departure from normal development, while only 12.8% of the full term controls did so. In those premature babies with birth weights under 1501gms. the incidence of neurological or intellectual defects was 50% (Knobloch et al., 1956; 1962). McDonald (1962) and Lubchenco et al. (1963) found similar results. Meanwhile, in Edinburgh a series of controlled prospective studies by Drillien (1961; 1964) showed that both IQ and developmental quotient fell with decreasing birth weights. About 90% of the children weighing less than 1360 gms. at birth had IQ's less than 100, and 22% had major physical handicaps.

Although these studies established a clear relationship between low birth weight and neurological or intellectual problems, the need for separating preterm infants of less than 2500 gms. or "true prematures" from the 30% of low birth weight infants that are full term or small-for-dates was pointed out by Battaglia et al. (1967), Gruenwald (1965),and Lubchenco (1970) because of the different neonatal and infantile morbidity and mortality rates of the two groups. Infants that are small-for-dates have morbidities that can be grouped into one of three categories: those associated with intrauterine infections, those associated with congenital anomalies, and those associated with intrauterine malnutrition.

A follow-up study of 45 small-for-dates infants was done at the University of Kentucky Medical Center. At ages one to four, one-third of the infants were less than the tenth percentile in weight; one-fifth showed a moderate developmental lag on screening examination; and one-ninth had congenital anomalies (Beargie et al., 1970). Van den Berg et al. (1966) compared low weight infants with short gestational ages with similar low weight infants of long gestational ages and found that the true prematures had a higher risk of neonatal mortality but within a few months were healthier than the small-for-dates infants who had a higher incidence of congenital anomalies. IQ tests of all babies weighing less than 2500 gms. born in Aberdeen, Scotland in 1948 showed that the IQ of those infants who were small-for-dates was much lower than the IQ of infants delivered after less than 36 weeks gestation (Baird, 1957). Although small-for-dates infants do better than true prematures neonatally (lower incidence of respiratory distress syndrome), they do have higher neonatal mortality rates than infants of the same gestational age who have appropriate birth weights. Clearly, small-for-dates infants are different from both other low birth weight infants and normal infants.

The relationship of the increased incidence of congenital anomalies to the morbidity of small-for-dates infants was further explored by Drillien (1970) in a study of 65 children all with congenital anomalies and all with birth weights less than 2000 gms. Suspected mental or neurologic defects occurred more frequently in the small-for-dates infants than in the true prematures, although the differences were not statistically significant. Drillien concluded that the increase in mental and neurologic

impairment in small-for-dates infants was due largely to association with the increased congenital anomalies present. She hypothesized that the mental and neurologic defects were also

> due to developmental malformations of the central nervous system, possibly at the cellular level, or that the adverse factor in early embryonic life which was responsible for the congenital anomaly also initiated some disturbance in body and brain growth. (Drillien, 1970)

Although, many such infants may represent a primary still undiscovered fetal malformation as Drillien suggests, some small-for-dates infants are clearly the result of intrauterine infections as evidenced by the 1963 rubella epidemic (Hughes, 1970). In addition, data in sheep show that intrauterine growth retardation could be produced experimentally by gradual embolization of the utero-placental vascular bed (Creasy et al., 1972). Similarly, in humans the higher incidence of small-for-dates babies after pregnancies complicated by vascular disorders such as pre-eclampsia (Bacola et al., 1966) still points to maternal or placental insufficiency as a major cause of small-for-dates infants, and it does not seem reasonable at present to exclude any of the possibilities.

D. Child Development after Pre-eclamptic Pregnancies

Not only is the physical and mental development of children directly related to their birth weights, but it also related to complications occurring in the mother during the pregnancy. Retrospective studies of children with cerebral palsy, epilepsy, mental deficiency and reading disorders showed a significant association with complications of pregnancy producing relative hypoxia such as pre-eclampsia and bleeding rather than mechanical ones such as forceps deliveries (Lilienfeld et al., 1951; 1954; Kawi et al., 1958; Pasamanick et al., 1955).

Although a prospective study by Creamer (1955) did not confirm these findings, other prospective studies were generally supportive. In a follow-up study of 103 children at ages three to six whose mothers suffered from late pre-eclampsia, 18% suffered from definite mental and physical developmental disorders and EEG abnormalities, while 13% had borderline developmental abnormalities (Scholz et al., 1968). Abnormalities were most prevalent among children whose mothers had severe pre-eclampsia. Scholz et al. compared these results to those of Bendl et al. who in a similar study found the incidence of such disorders to be 48%. Searching for an anatomic explanation for these findings, Naeye (1966) found mean brain weight in autopsied toxemic infants to be 81% that of controls and hypothesized that decreased placental blood flow caused fetal malnutrition and that was in turn responsible for decreased brain weight and the neonatal hypoglycemia in toxemic infants previously described by Cornblath et al., (1959). Schulte et al. (1971) also felt that the maturation of the nervous system was adversly affected in toxemia when in 21 small-for-dates infants of toxemic mothers, they found decreased muscle tone and excitability.

In the early stages of the current study, it became apparent that it was necessary to make complications of pregnancy a controlled variable, and it was decided to study primarily children whose mothers had pre-eclampsia. Pre-eclampsia was chosen because both the estriol excretion patterns and the neurological and intellectual sequelae of this complication have been well studied separately but never in a combined fashion. However, just as an interpretation of low estriol excretion patterns in pre-eclamptic patients must account for fetal weight influences, investigation of the

neurological and mental development of children of pre-eclamptic pregnancies must take into consideration the increased incidence of children in this group who had low birth weight and were small for dates. Many workers found this association (Brown et al., 1946; Maqueo et al., 1964), although some found the increased incidence of small-for-dates infants only if the pre-eclampsia was severe or of long duration (Baird et al., 1957; Gruenwald, 1963; Usher, 1970; Walker, 1965; Bacola et al., 1966). In fact, the average birth weight in a group of severe toxemics was found to be lower than in a group of mild toxemics (2068 gms. versus 2596 gms.) (Maqueo et al., 1964). The significance of this difference can be seen in a prospective study of low birth weight infants who were products of pre-eclamptic pregnancies. Only 1 of 6 infants with birth weight less than 1500 gms. was of normal intelligence at follow-up, while 6 of 7 with birth weight of 1500 to 2500 gms. were of normal intelligence (Bacola et al., 1966).

One obvious question was whether the neurological and mental defects were associated only with toxemia's tendency to produce low birth weight infants or with some other more direct effect of toxemia. Knobloch et al. (1962) looked at this question retrospectively in a group of children all of whom had mature birth weights. Although no association between toxemia and gross defects such as cerebral palsy and epilepsy was present, toxemia was still associated with minor defects, such as learning and behavior disorders. A prospective study of children of mature birth weight showed that children exposed to toxemia did less well than controls in cognitive function and behavior (Buck et al., 1969).

Neither of these studies distinguished between mild and severe toxemia or looked specifically at controlled groups of small-for-dates infants. Beargie et al. (1970) who did so found that 7 of the 8 small-for-dates infants delivered from mothers with mild ,short duration pre-eclampsia were well-grown children and in fact "better grown" than the other small-for-date newborns in the study. Unfortunately, they did not study any mothers with severe pre-eclampsia of long duration so that it was impossible to generalize about pre-eclampsia from their study. Another indication that pre-eclampsia itself may not have been responsible for the increased incidence of neurological and intellectual defects was the retrospective study by McDonald (cited in Stimmler, 1970) of 220 small-for-dates infants. He found a higher incidence of mental retardation and epilepsy after pregnancies without pre-eclampsia than after those with pre-eclampsia, but again it was unclear whether the mothers had mild or severe symptoms. Two very important questions must be raised about both of these studies: what associated factors were responsible for the low weight of the small-for-dates infants without pre-eclampsia and what influence did these factors have on later development?

From all these studies, one can tentatively conclude that maternal toxemia, particularly if severe, was associated with a high incidence of small-for-dates offspring. It is still unclear whether the neurological and mental defects of pre-eclampsia were related more to the accompanying high incidence of small-for-dates infants or to a more direct effect of toxemia itself. The present study—which correlates maternal estriol excretion (an assessment of feto-placental function) with the subsequent development of offspring—may help to clarify these questions.

II. PATIENTS AND METHODS

Pregnancies were studied representing 21 mothers and 21 live births. Patients were selected on the basis of urinary estriol patterns and the availability of their children for follow-up examination. All of the mothers were cared for and delivered at Yale-New Haven Hospital.

The 24 hour maternal urinary estriol determinations were done by the rapid assay of total estrogen content utilizing a Kober-Ittrich color reaction and estriol standards as described by Cohen (1966). The method measures total estrogen content, but values are expressed as mg. estriol equivalents excreted per 24 hours, since 90% of all estrogen excreted in the urine by a pregnant woman is in the form of estriol conjugates (Taylor et al., 1965b; Greene et al., 1963). Estriol excretion patterns described in this paper, therefore, actually represent the patterns of total estrogen excretion, but the term estriol is used, since increases or decreases in estriol excretion are the causes of the fluctuations measured by this method. The normal range of values ±2 S.D. using this method at Yale-New Haven Hospital are those between the dashed lines shown on the graph in Figure II. Values below 12 mg.per 24 hours after the thirty-fourth week are felt to indicate fetal jeopardy. The minimum number of estriol determinations in each pregnancy was two, and all patients had estriol determinations within a week of delivery except one.

Patients were divided into three groups. One category of 13 patients represents all of the mothers with either chronically low or precipitously dropping estriols who delivered at Yale-New Haven Hospital since 1966, when estriols were first done, and whose children were available for follow-up. Those considered to have low estriols had at least two values

prior to delivery less than 12 mg. per 24 hours, while those with falling estriols had a drop of at least 60% just prior to delivery. Those unavailable for follow-up had all moved and could not be contacted. Of these 13 patients, 8 mothers suffered from pre-eclampsia during their pregnancies and constitute Group I, while the remaining 5 had other pregnancy complications and constituted Group III.

It was decided to establish a control group with toxemia, and therefore Group II consisted of 8 patients who all had normal urinary estriols and pre-eclampsia. This control group was selected by finding all the mothers who had both pre-eclampsia and estriols that were clearly normal, that is, final determinations above 12 mg. per 24 hours in the 48 hours before delivery. One of the controls had her last estriol determination during the week prior to delivery, but in that week three determinations were above 30 mg. per 24 hours, and she was felt to have a normal estriol pattern. These 8 patients were the only ones at Yale-New Haven Hospital who met these rigid criteria, and the children of all were examined.

Data were collected concerning maternal obstetric history (gestational age from menstrual history),medical history, complications of pregnancy, labor and delivery, as well as socioeconomic status (lower, lower-middle, middle, upper-middle, and upper). Socioeconomic status was estimated from vocational and housing data. In addition, data regarding infant birth weight, gestational age, and neonatal course were obtained from hospital records. Birth weight percentiles for gestational age were determined by using the Colorado Intrauterine Growth Charts (Lubchenco et al., 1966), and infants were considered small for dates if their birth weights were less than 10% of those expected for their estimated obstetric gestational ages.

Pre-eclampsia in the mother was classified as mild or severe according to the criteria of Hellman et al. (1971). Mild pre-eclampsia occurred after the twentieth week of pregnancy with elevation of systolic or diastolic blood pressure to $^{140}/90$ on at least two occasions with or without 1-2 + proteinuria and/or edema. Severe pre-eclampsia occurred if blood pressure rose to $^{160}/110$ or the patient had 3-4 + proteinuria or cerebral or visual symptoms. The patients were also categorized as to whether the pre-eclampsia occurred before the thirtieth week of pregnancy (long duration) or after (short duration).

Follow-up examinations of the infants and interviews of mothers were performed by the author in the pediatric clinic of Yale-New Haven Hospital. The infants were aged 7 months to 4 years, although 20 of 21 infants were under age 2. Examination included interim history including motor milestones, a physical and neurological exam including measurements of height, weight, and head circumference and the administration of the Denver Developmental Screening Test (DDST) (Frankenburg and Dodds, 1967). Percentiles of height and weight were determined according to the Harvard Charts (Nelson et al., 1969) and of head circumference according to Nellhaus (1968). Hospital charts contributed interim history for most of the infants.

The Denver test is a simple screening test for evidence of slow development in infants and preschool children. The test covers four functions: gross motor, language, fine-motor adaptive, and personal-social. The age norms for language development may be slightly later in lower socio-economic classes (Frankenburg and Dodds, 1967). The test is neither an intelligence test nor a diagnostic tool but simply allows the examiner to determine whether or not a child's development is within

the normal range. Each child's performance on the DDST was rated 1 if clearly normal, 2 if questionable, and 3 if clearly abnormal according to the criteria of Frankenburg and Dodds (1967). Four children (case nos. 3, 15, 17, and 18) were also evaluated independently at the Yale Child Study Center,and the results agreed with those found using the Denver test.

III. RESULTS

The data collected on the three groups of patients can be seen in Tables I-IV. Group I consists of all those mothers who had pre-eclampsia and low or falling urinary estriols. Group II serves as a control for Group I and consists of all those mothers with pre-eclampsia and normal urinary estriols. Group III represents an additional group of patients with low urinary estriols and other complications of pregnancy such as cyanotic congenital heart disease, Rh incompatibility,or diabetes mellitus.

Table I shows the data for maternal age, race, socioeconomic status, obstetric history, maternal disease,and delivery in the three groups. Mothers in Group I had more obstetric complications both in this pregnancy and in previous ones than mothers in Group II. Table II shows the maternal estriol excretions of the three groups by week of gestation determined as total estrogen and expressed as mg. estriol equivalents excreted per 24-hour urine. Low estriol excretion was further subdivided into two categories: chronically low and precipitously dropping estriols. The low or falling estriol values of Group I are represented graphically in Figure II,while the normal values (± 2 S.D.) are those between the dashed lines. Table III gives the birth data for the infants in the three groups including weight, Apgar, gestational age estimated from newborn physical examination, and neonatal complications. Birth weights were clearly lower in the groups

with low estriol excretion. Table IV shows the results of the follow-up examination for the three groups including interim histories, measurements, physical and neurological examinations, behavior and milestone histories, and the results of developmental screening tests. Five infants in Groups I and III were abnormal while none in Group II were abnormal. These findings will be discussed in the following section. Table V presents a summary of the infant follow-up findings along with the important variables of maternal disease, estriol excretion pattern, and infant birth weight percentile.

TABLE I: MATERNAL DATA

Group I: Low Urinary Estriols with Pre-eclampsia

Case No.	Age	Marital Status [a]	Race	Socio-economic Status [b]	Obstetric History	Chronic Maternal Disease	Pre-eclampsia (severity duration)	Delivery and Complications [c]
Chronically Low:								
1	16	S	N	L	G2 P1 LC1 1 premature	chronic glomerulonephritis	severe, short	L: failed induction D: C/S Ind: fetal distress ↓ estriol
2	36	M	C	M	G1 P0 LC0 previous difficulty conceiving	none	severe, short	D: C/S Ind: ↑BP, ↓ estriol Comp: oligohydramnios bleeding, poor uterine growth
3	36	M	C	LM	G4 P3 LC3 previous pre-eclampsia	hypertension	superimposed severe, long	L: spontaneous D: vaginal Comp: precipitous delivery
4	33	M	C	M	G2 P1 LC0 1 stillbirth previous pre-eclampsia	chronic pyelonephritis	severe, long	D: C/S Ind: ↓ estriol uncontrolled BP
5	40	Sep.	N	LM	G6 P4 LC4 stillborn twins	none	mild, long	L: induced after failure with PGA D: vaginal Ind: ↓ estriol
Precipitously Dropping:								
6	29	M	C	LM	G3 P1 LC1 1 abortion previous pre-eclampsia	hypertension schizoid personality	superimposed mild, short	L: induced D: vaginal Ind: poor obstetric history ↓ estriol, ↓ fetal movement
7	32	S	N	L	G6 P5 LC5 previous pre-eclampsia Rh Neg.	asthma	severe, short	L: failed induction D: C/S Ind: ↑ BP, ↓ estriol Comp: UTI, bleeding, anemia, cord around leg
8	32	M	C	LM	G9 P7 LC7 1 abortion previous pre-eclampsia	chronic renal disease	mild, short	L: induced D: vaginal Ind: ↓ estriol

a. S= single; M= married; D= divorced; W=widow; Sep= separated

b. C= Caucasian; N=Negro

c. L= lower; LM=lower middle; M=middle; UM= upper middle; U= upper

TABLE I: MATERNAL DATA

Group II: Normal Urinary Estriols with Pre-eclampsia

Case No.	Age	Marital Status[a]	Race[b]	Socio-economic status[c]	Obstetric History	Chronic Maternal Disease	Pre-eclampsia (severity duration)	Delivery and Complications[d]
9	24	S	N	L	G3 P2 LC2	chronic renal disease with hypertension	superimposed severe, short	L: spontaneous D: vaginal Comp: meconium staining
10	35	W	N	LM	G3 P2 LC2	hypertension	superimposed severe, short	L: induced D: vaginal Ind: ↑ BP Comp: UTI
11	25	Sep.	N	L	G1 P0 LC0	anemia minimal hydronephrosis	mild, short	L: failed induction D: C/S Ind: PROM, fetal distress Comp: amnionitis, cord around neck
12	17	D	N	L	G1 P0 LC0	class A diabetes mellitus anemia	mild, short	L: induced D: vaginal with vacuum Ind: ↓estriol, fetal distress Comp: UTI, fetal bradycardia
13	21	S	N	L	G1 P0 LC0	none	mild, short	L: spontaneous D: vaginal
14	33	M	N	LM	G3 P2 LC2 previous pre-eclampsia	none	mild, short	L: induced D: vaginal with low forceps Ind: post dates Comp: cord around neck, thick meconium
15	22	M	N	M	G1 P0 LC0	none	severe, long	L: induced D: vaginal with mid-forceps Ind: inertia Comp: meconium stain
16	24	S	N	L	G3 P2 LC2 previous pre-eclampsia	hypertension	superimposed severe, short	D: C/S Ind: previous C/S Comp: polyhydramnios

a.S= single; M-married; D-divorced; W= widow; Sep- separated

b.C- Caucasian; N= Negro

c.L=Lower; LM= lower middle; M= middle; UM= upper middle; U= upper

TABLE I: MATERNAL DATA

Group III: Low Urinary Estriols with Other Complications

Case No.	Age	Marital Status[a]	Race[b]	Socio-economic status[c]	Obstetric History	Chronic Maternal Disease	Pre-eclampsia (severity duration)	Delivery and Complications
Chronically Low:								
17	20	M	C	UM	G1 P0 LC0	tetralogy of fallot (Blalock)	retarded uterine growth	L: induced D: vaginal with low forceps Ind: maternal symptoms, ↓ estriol Comp: cord around shoulder
18	29	M	C	M	G4 P1 LC1 2 abortions previous pre-eclampsia	tetralogy of fallot (Blalock) chronic renal disease	Rh incompatibility	L: spontaneous D: vaginal with low forceps Ind: ↓maternal pO_2
19	27	M	N	M	G2 P1 LC1	none	retarded uterine growth	L: spontaneous D: frank breech assisted
20	34	M	N	LM	G6 P1 LC1 4 abortions	diabetes mellitus class B	minimally elevated blood pressure	L: failed induction D: vaginal with vacuum Ind: ↓estriol
Precipitously Dropping:								
21	29	M	C	M	G4 P3 LC2 1 abortion	none	Rh incompatibility	L: spontaneous D: vaginal with low forceps Comp: fetal distress placental abruption cord around neck

a. S= single, M= married; D= divorced; W= widow; Sep= separated

b. C= Caucasian; N=Negro

c. L= lower; LM= lower middle; M= middle; UM= upper middle; U= upper

TABLE II: ESTRIOL EQUIVALENTS[e] BY WEEK OF GESTATION[f]

Group I: Low Urinary Estriols with Pre-eclampsia

Case No.	Calculated Gestation at Delivery (weeks)	Gestational Week 32	33	34	35	36	37	38	39	Category	Interval (days) Last Estriol and Delivery
Chronically Low:											
1	36		4.4	1.6 1.8	1.6 2.0	3.4				low	3
2	36				2.3	5.6				low	1
3	37			6.3		10.1	5.6			low	1
4	35			6	3.8					low	1
5	39	6.0 18.2 9.5	4.6	8.8 11.6	4.5	failed induction		13.2	11.4	low	1
Precipitously Dropping:											
6	36	7.0	15.8	22.0	23.7	10.9				drop	1
7	38						23.7 28.0 21.8	8.6		drop	1
8	38			28.4	18.8 22.9	8.1	7.7			drop	5

e. measured as total estrogen but expressed as mg. estriol equivalents per 24-hour urine, since estriol represents 90% of total estrogen excreted during late pregnancy

f. final value before delivery is underlined

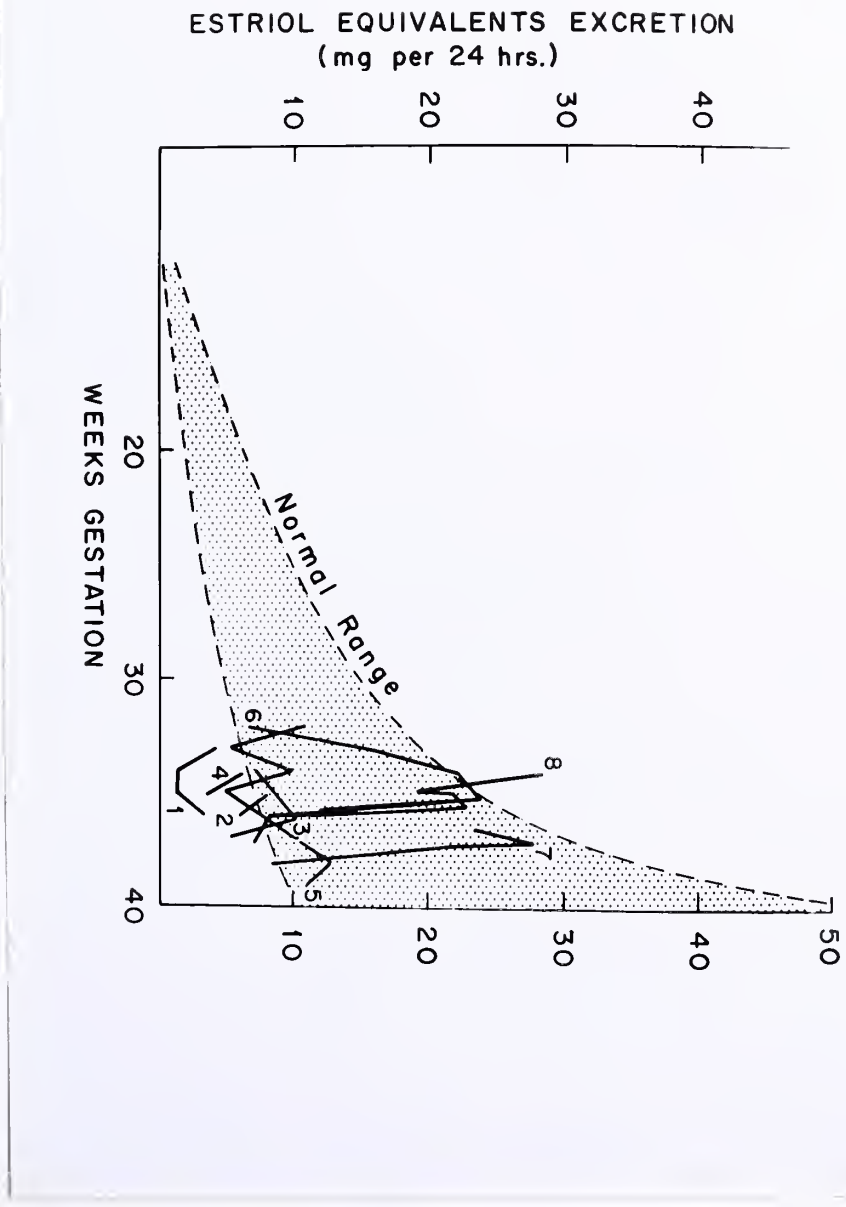

Figure II. Estriol excretion of group I. Case nos. 1-5, patients with chronically low estriols and pre-eclampsia; case nos. 6-8, patients with precipitously dropping estriols and pre-eclampsia. Normal values (± 2 S.D.) are between the dashed lines. All values of Group II fall within the normal range.

TABLE II: ESTRIOL EQUIVALENTS[e] BY WEEK OF GESTATION[f]

Group II; Normal Urinary Estriols with Pre-eclampsia

Case No.	Calculated Gestation at Delivery (weeks)	Gestational Week 29	30	31	32	33	34	35	36	37	38	39	40	41	Category	Interval (days) Last Estriol and Delivery
9	38								46.8	41.0	40.3				normal	2
10	39			10.5	16.3	13.8 15.5	13.0 13.3		12.5 17.3		30.4	36.5 32.7			normal	1
11	40									21.5	9.7 38.5	54.9 38.7 38.3			normal	7
12	40									32.9	34.7	46.2	27.5 23.9		normal	0
13	37							31.5	40.3	45.3					normal	0
14	41									29.1	11.2 12.3 40.6	25.8 42.9	24.4 39.8 28.5	25.7	normal	1
15	42												12	20.8	normal	2
16	40							41.7	11.1 42.5	39.6 32.6	54.0 44.1	28.9 26.8	30.0		normal	4

e. measured as total estrogen but expressed as mg. estriol equivalents per 24-hour urine, since estriol represents 90% of total estrogen excreted during late pregnancy.

f. final value before delivery is underlined.

TABLE II; ESTRIOL EQUIVALENTS[e] BY WEEK OF GESTATION[f]
Group III; Low Urinary Estriols with Other Complications

Case No.	Calculated Gestation at Delivery	Gestational Week 29	30	31	32	33	34	35	36	37	38	39	Category	Interval (days) Last Estriol and Delivery
Chronically Low:														
17	39						1.2 2	3.5	3.7 2.7 2.5	6.9 2.6 3.8	6.3 3.8 6.3 7.8 5.4 4.9	3.8 6.1 6.4 6.6 <u>3.1</u>	low	1
18	36	4.8 5.3	3.5	4.3	6.2 6.6	5.2 5.0 9.9	6.7 4.6 5.6 5.8	4.7 8.6	4.7 6.0 <u>6.2</u>				low	2
19	38								9.4	<u>10.7</u>			low	6
20	38		3.8	2.1	1.7	8.8	5.5	4.4	7.3 10.0	<u>6.7</u>			low	2
Precipitously Dropping:														
21	41							33.1	22.3 27.1	28.0 26.0 24.9	28.0 36.5 39.1	<u>8.1</u>	drop	14

e. measured as total estrogen but expressed as mg. estriol equivalents per 24-hour urine, since estriol represents 90% of total estrogen excreted during late pregnancy.

f. final value before delivery is underlined.

TABLE III: BIRTH DATA

Group I: Low Urinary Estriols with Pre-eclampsia

Case No.	Sex	Gestation at Delivery-P.E. (weeks)	Birth Weight grams	Birth Weight % tile[g]	Apgar 1 min/5 min.	Neonatal Condition and Course
Chronically Low:						
1	M	35	885	<<10*	3/5	apneic at birth, tremulous, fed poorly, pneumonia age 2 months, small head circumference
2	M	36	1350	<10*	6/8	hypoglycemic - day 1, jaundice day 4
3	M	36	1875	<10*	2/5	apneic, intubation at birth, hypoglycemia - day 2, jaundice - day 5, tremulous, poor suck, hemangioma
4	M	34	1400	<10*	7/9	minimal RDS-day 1, hypertonic, jittery
5	F	37	2755	25	8/9	jittery, poor rooting reflex
Precipitously Dropping:						
6	M	36	1900	10	9/9	normal
7	M	39	3005	50	8/9	normal
8	F	39	2980	50	8/9	hypoglycemia- day 1, cyanosis- day 1, seizures- day 2, hypertonic, poor grasp reflex
Group II: Normal Urinary Estriols with Pre-eclampsia						
9	F	40	3045	50	9/9	enlarged liver, heart murmur, Silverman 0 at birth
10	M	40	3465	75-90	9/9	apneic at birth, ↓motor activity with slow reflexes
11	F	40	2925	25-50	3/4	intubated at birth, Silverman 0, sepsis (maternal amnionitis)
12	M	40	3250	50	9/9	hypoglycemia- day 2, jaundice- day 2
13	M	38	3390	75-90	9/9	umbilical hernia
14	M	40	3825	>90	9/9	generalized rash (monilia)
15	F	40	3890	>90	9/9	jittery, ↑tone with clonus in right extremities, tachypnea, distended abdomen, twitching, normal EEG
16	F	40	3630	75-90	9/9	normal

g. Lubchenco, 1966; asterisk indicates small-for-dates infant

TABLE III: BIRTH DATA

Group III; Low Urinary Estriols with Other Complications

Case No.	Sex	Gestation at Delivery-P.E. (weeks)	Birth Weight grams	Birth Weight % tile[g]	Apgar 1 min/5 min.	Neonatal Condition and Course
Chronically Low:						
17	F	37	1780	<<10*	8/9	jaundice- day 4
18	F	36	1970	10	9/9	intubated at birth, jaundice- day 3 (Rh incompatibility)
19	F	38	1200	<10*	5/7	jaundice- day 4, RDS- day 2, lethargic, floppy
20	M	38	3370	>75	7/9	RDS- day 1, jaundice- day 3, hyponatremia, "large for dates", hemangioma right eyelic
Precipitously Dropping:						
21	F	40	3070	25-50	1/8	apneic at birth, ↓heart rate, enlarged spleen (Rh incompatibility)

g. Lubchenco, 1966; asterisk indicates-small-for-dates infant

TABLE IV: INFANT FOLLOW-UP EXAMINATION

Group I: Low Urinary Estriols with Pre-eclampsia

Case No.	Age at exam (mos.)	Weight kgms/%[h]	Height cm/%[h]	H.C. cm/%[i]	Interim History	Physical Exam	Behavior History	Gross Motor Milestones	DDST[j] Gross Motor	Fine Motor	Personal Social	Language	Summary Rating
Chronically Low:													
1	22	9.6/<<3	83/10-25	45/<<3	external rotation left leg, hypertonic, pneumonia	abduction of left hip and ankle, ↑ muscle tone, ↓ strength normal skull X rays	normal	normal	P	P	P	P	1
2	28	12.2/10-25	88.5/25	48/10	pneumonia, delayed development	no dominance	hyperactive, ↓attention span	slow	P	P	P	Fx2	3
3	50	16.4/50	95.5/<3	50.5/<90	ketogenic hypoglycemia, seizure disorder (status X1), pneumonia, hyperactive, slow development	normal	hyperactive	slow	F	F	P	Fx2	3
4	21	10/<3	74/<3	49/50	normal	right metatarsus adductus	normal	normal	P	P	P	P	1
5	13	9/10-25	75/50	44/2-50	normal	normal	normal	normal	P	P	P	P	1
Precipitously Dropping:													
6	17	13/90	77.5/<10	49/90	asthma, right esotropia	right esotropia	normal	normal	P	P	P	P	1
7	32	17.7/>97	96/90	52/>90	asthma	normal	normal	normal	P	P	P	P	1
8	13	10.2/50-75	76.5/75	46.5/50	pneumonia	normal	normal	normal	P	P	P	F[k]	1

h- %tile from Harvard charts

i- head circumference %tile from Nellhaus, 1968

j-Frankenburg and Dodds, 1967, p= pass, F= fail; summary rating=1, clearly normal; 2, questionable; 3, clearly abnormal

k-Children from lower socioeconomic classes pass language items at older ages;by itself, delayed language function does not indicate developmental delay

TABLE IV: INFANT FOLLOW-UP EXAMINATION
Group II: Normal Urinary Estriols with Pre-eclampsia

Case No.	Age at exam (mos.)	Weight kgms./%[h]	Height[h] cm/%	H.C.[i] cm/%	Interim History	Physical Exam	Behavior History	Gross Motor Milestones	DDST[j] Gross Motor	Fine Motor	Personal Social	Language	Summary Rating
9	7	7.3/25-50	65/25	44/50	asymptomatic VSD, dermoid cyst left orbit, varus deformity of feet	systolic murmur, dermoid cyst left orbit	normal	normal	P	P	P	P	1
10	16	10/10	76/3-10	48/25	anemia (lead ingestion)	normal	normal	normal	P	P	P	P	1
11	21	14/>90	86/75	50/90	pneumonia	normal	normal	normal	P	P	P	P	1
12	21	12/50-75	84/25-50	48/25	normal	normal	normal	normal	P	P	P	P	1
13	22	12/>50	85/75	49/50	right metarsus adductus	right metatarsus adductus	normal	normal	P	P	P	P	1
14	13	14/>97	85/>97	51/>97	normal	normal	normal	normal	P	P	P	P	1
15	23	14/90	90/90	50/>90	normal	normal	normal	normal	P	P	P	P	1
16	21	10/10-25	83/25-50	46/3-50	normal	small umbilical hernia	normal	normal	P	P	P	P	1

h- %tile from Harvard charts
i- head circumference %tile from Nellhaus, 1968
j-Frankenburg and Dodds, 1967; p= pass; summary rating-1, clearly normal; 2, questionable; 3, clearly abnormal

TABLE IV: INFANT FOLLOW-UP EXAMINATION

Group III: Low Urinary Estriols with Other Complications

Case No.	Age at exam (mos)	Weight kgms/%[h]	Height cm/% [h]	H.C. cm/%[i]	Interim History	Physical Exam	Behavior History	Gross Motor Milestones	DDST[j] Gross Motor	Fine Motor	Personal Social	Language	Summary Rating
Chronically Low:													
17	13	8.4/3-10	72/10-25	43/<< 3	retarded bone age	normal	normal	normal	P	P	P	P	1
18	11	7.5/3-10	70/10-25	44.5/10-50	normal	normal	normal	normal	P	P	P	P	1
19	10	8.6/25-50	70/50	45/50	normal	normal	normal	normal	P	F	P	P	2
20	13	8.5/<3	77.5/50-75	44.5/3-50	poor weight gain	normal	normal	normal	P	P	P	P	1
Precipitously Dropping:													
21	8	8.7/75	69/75	43/50	normal	normal	normal	normal	P	P	P	P	1

h- %tile from Harvard charts
i- head circumference %tile from Nellhaus, 1968
j- Frankenburg and Dodds, 1967; p= pass, F= fail; summary rating- 1, clearly normal; 2, questionable; 3, clearly abnormal

TABLE V: SUMMARY PROFILE OF EACH CHILD

Case No.	Pre-eclampsia (severity, duration)	Last Estriol Before Delivery (mg./24 hrs)	Estriol[1] Excretion Trend	Calculated Gestation at Delivery (weeks)	Birth Weight (gms./%tile)[m]	Summary of Follow-up Findings
Group I: Low Urinary Estriols with Pre-eclampsia						
Chronically Low:						
1	severe, short	3.4	low	36	885/≪10*	mic rocephaly with ↓ muscle strength, ↓ tone and valgus deformity left leg.
2	severe, short	5.6	low	36	1350/<10*	hyperactive with ↓attention span, delayed development (8 month lag)
3	superimposed severe, long	5.6	low	37	1875/<10*	seizure disorder, ketogenic hypoglycemia, hyperactive, delayed development (one year lag), hemangioma
4	severe, long	3.8	low	35	1400/<10 *	right metatarsus adductus
5	mild, long	11.4	low	39	2755/25	normal
Precipitously Dropping:						
6	mild, short	10.9	drop	36	1900/10	right esotropia
7	severe, short	8.6	drop	38	3005/50	normal
8	mild, short	7.7	drop	38	2980/50	normal
GroupII: Normal Urinary Estriols with Pre-eclampsia						
9	superimposed severe, short	40.3	normal	38	3045/50	asymptomatic VSD, dermoid cyst
10	superimposed severe, short	32.7	normal	39	3465/75-90	normal
11	mild, short	38.3	normal	40	2925/25	normal
12	mild, short	23.9	normal	40	3250/50	normal
13	mild, short	45.3	normal	37	3390/75-90	right metatarsus adductus
14	mild, short	25.7	normal	41	3825/>90	normal
15	severe, long	20.8	normal	42	3890/>90	normal
16	severe, short	30.0	normal	40	3630/75-90	small umbilical hernia

1- measured as total estrogen but expressed as mg. estriol equivalents per 24-hour urine, since estriol represents 90% of total estrogen excreted during late pregnancy

m- Lubchenco, 1966; asterisk indicates small-for-dates infant

TABLE V: SUMMARY PROFILE OF EACH CHILD
Group III: Low Urinary Estriols with Other Complications

Case No.	Complication of Pregnancy	Last Estriol Before Delivery (mg./24 hours)	Estriol Excretion Trend [1]	Calculated Gestation at Delivery (weeks)	Birth Weight gms/%tile [m]	Summary of Follow-up Findings
Chronically Low:						
17	tetralogy of fallot retarded uterine growth	3.1	low	39	1780/<< 10*	small head circumference, retarded bone age
18	tetralogy of fallot Rh incompatibility	6.2	low	36	1970/10	normal
19	retarded uterine growth	10.7	low	38	1200/<10*	questionable developmental delay
20	diabetes mellitus class B	6.7	low	38	3370/>75	hemangioma right eyelid
Precipitously Dropping:						
21	Rh incompatibility	8.1	drop	41	3070/25-50	normal

1-measured as total estrogen but expressed as mg. estriol equivalents per 24-hour urine, since estriol represents 90% of total estrogen excreted during late pregnancy
m-Lubchenco, 1966; asterisk indicates small-for-dates infant

IV. DISCUSSION

The data of Groups I and II will be analyzed first in an attempt to understand what variables might explain the increased number of infants who did poorly in Group I. The data for these two groups will then be compared with those of Group III at the end of this section.

The interpretation of the data gathered in this study is limited by the small number of patients involved, the varying ages of the children at follow-up examination, and the absence of a double-blind protocol so that the investigator seeing the children was aware of maternal status. The number of patients was restricted by the number of years the estriol test has been done at this hospital and by the need for patients who conform to rigid criteria of estriol pattern and maternal disease.

Socioeconomic status, race, and age: More patients in Group II come from lower socioeconomic classes and more are Negro than in Group I, and therefore, one cannot say that the infants in Group I did poorly because of class or racial factors. In fact, the infants who did poorly represent both races and the lower, lower-middle, and middle socioeconomic classes represented in the two groups. However, the maternal age of patients in Group I is on the average (32) considerably older than that of patients in Group II (25). The 3 children who did poorly (case nos. 1,2,3) had mothers whose ages were 36,36, and 16, representing the very old and the very young.These data are in agreement with the fact that extremes of age are well-known risk factors in pregnancy (Drillien, 1964) and that the feto-placental unit in older women may be less able to maintain normal estriol levels until term.

Obstetric history: All of the mothers in Group I had poor obstetric histories, including previous pre-eclampsia, infertility problems,

abortions, stillbirths, or prematures. In contrast, only 2 of the 8 mothers in Group II (case nos. 14 and 16) had previous complications of pregnancies, and both had pre-eclampsia. In part, this difference reflects the fact that the women in Group II were younger and had had fewer pregnancies. In Group I, however, even those mothers pregnant for the first or second time had poor obstetric histories.

Chronic maternal disease: In both Groups I and II, 5 of the 8 mothers with pre-eclampsia had, in addition, pre-existing hypertension, renal disease, or diabetes mellitus, all of which are by themselves associated with low estriol excretion. Of the mothers of the 3 infants who did poorly, 1 had pre-existing renal disease, 1 had pre-existing hypertension, and 1 had no chronic disease before developing pre-eclampsia. Therefore, it does not appear that chronic maternal disease influenced which infants did poorly or which mothers had low estriol excretion.

Severity and duration of pre-eclampsia: In Group I, 7 of the 8 patients had either severe pre-eclampsia, pre-eclampsia of long duration, or pre-eclampsia superimposed on chronic hypertension, while one-half of the patients in Group II had none of these. In addition, the mother of 1 infant in Group I (no. 3) who did poorly had all three complications: severe pre-eclampsia of long duration superimposed on chronic hypertension. All three factors are known to worsen the prognosis for the infant, and it appears that these factors influence the estriol production by the feto-placental unit. Earlier studies have shown that estriol production is only minimally influenced by blood pressure (Michie, 1967),and one may speculate that blood flow changes in pre-eclampsia are responsible for the drop in estriol excretion (Gant et al.,1971).

Labor and delivery: Delivery was by Caesarean section in 4 mothers in

Group I, while this was only necessary for 2 mothers in Group II. However, type of delivery did not influence which children were doing well when seen at follow-up examination. Further ramifications involving labor and delivery are too complicated to be clarified in this study.

Birth weight: Half of the infants in Group I were small for dates (nos. 1,2,3, and 4) while none of the infants in Group II were small for dates. In fact, 5 of the 8 infants in Group I had birth weights less than 2000 gms., while all of the infants in Group II weighed more than 2900 gms. In addition, 3 of the 4 infants who were small for dates were doing poorly on follow-up exams, and the other one had a minor congenital anomaly of the foot. The fifth child of birth weight less than 2000 gms. in Group I had strabismus, an anomaly found in 45% of low birth weight infants studied by Lubchenco et al. (1963). The well-grown normal birth weight babies of Group II were doing relatively well on follow-up exam: one child had a similar minor anomaly of the foot, another child had a dermoid cyst and an asymptomatic ventricular septal defect, and a third had an umbilical hernia.

Although there does not appear to be a sharp dividing line in absolute estriol values between small-for-dates infants and better-grown infants, clearly, mothers with low urinary estriols frequently give birth to low weight infants, and in turn these infants do poorly. The questions that remain are why do some mothers with abnormal urinary estriols give birth to normal weight infants and how do these babies do on follow-up? The data may provide some clue. Of the babies born to mothers with chronically low estriol excretion (nos. 1,2,3,4, and 5), 4 of 5 were small for dates and 3 of the 4 did poorly. In contrast, of the babies delivered because of precipitously dropping maternal estriol excretion (nos. 6,7, and 8), none were small for dates, and 2 of the 3

weighed more than 2500 gms. at birth, although the third child's birth weight was exactly at the 10th percentile for gestational age. From the opposite viewpoint, 3 of the 4 well-grown infants in Group I were born to mothers with precipitously dropping, rather than chronically low, estriols. It appears that precipitously dropping estriols are helping obstetricians to salvage babies who grow and develop normally while infants born after chronically low estriols frequently have demonstrable gross neurological defects by age 4.

A complicating factor is the gestational age of these infants. All the infants with birth weights less than 2000 gms. had a calculated gestational age less than 37 weeks, while the duration of gestation for all the remaining infants exceeded this. The pregnancies of 3 of the 4 mothers of small-for-dates infants were terminated by Caesarean section because of low estriols and the fear of fetal demise, and it is doubtful if allowing the pregnancy to continue in spite of the low estriols would have led to better-grown babies rather than fetal demise. However, it seems that in pregnancies with chronically low estriol excretion , the low values do not indicate fetal demise but rather intrauterine growth retardation. In the latter cases, since these babies don't do well after delivery, a hypothetical alternative to interrupting pregnancy might be an attempt to treat the growth retardation in utero. Intra-amniotic amino acid infusions which the fetus could swallow and assimilate via the gastrointestinal tract might partially bypass the problem of placental insufficiency and reverse the fetal malnutrition. The finding that mothers with lower blood amino acid levels gave birth to lighter, shorter babies with smaller cranial volumes than mothers with higher blood amino acid levels suggests that fetal development is stunted when amino acid supplies are diminished and provides some data to support this

alternative mode of therapy (Moghissi et al., 1969)

Neonatal complications: No difference could be noted in neonatal complications between the babies of Groups I and II nor were any differences noted between those babies who were doing well on follow-up and those who were not. Neonatal hypoglycemia has been noted to be associated with pre-eclampsia (Cornbath et al., 1959). In the total of 16 patients in Groups I and II studied here, only 4 of the 16 infants had neonatal hypoglycemia, and 2 of the 4 were small for dates. Other neonatal complications were apnea (nos. 1,3,10, and 11), sepsis (no. 11), tremulousness (nos. 1,3,4, 6 and 15), and jaundice (nos. 2,3, and 12).

Urinary estriol excretion: The differences between the infants born to mothers with low urinary estriols and those born to mothers with normal estriols have already been discussed. Because of small numbers,it is very difficult to compare the 5 patients with chronically low estriols with the 3 patients with precipitously dropping estriols. An attempt has already been made with respect to the different effects on birth weight (see pages 38-39).It also appears that precipitously dropping estriols occur in younger mothers with milder pre-eclampsia of short duration; in fact, in 2 of the 3 patients with a precipitous fall (nos. 6 and 8), the drop coincided with the time of onset of the pre-eclampsia. The precipitous drop in estriols in these patients might have been due either to placental insufficiency or changes in renal blood flow or to other factors. However, if the data presented here are valid, the reason for the drop may not matter, for if these infants are promptly delivered after the fall occurs, the prognosis for the later development of healthy children is uniformly good.

Group III: This group is quite diverse and represents only 5 patients, but one can use the data from such a group to see which conclusions based on patients with low urinary estriols and pre-eclampsia hold true for patients with low urinary estriols and other chronic diseases. This group is similar in racial and socioeconomic distribution to Group I, but is slightly younger in average age (28). There is also a lower frequency of previous obstetric complications. No Caesarean sections were done, but one child was a breech delivery, and this is a known risk factor (Muller et al., 1971). This child did poorly on follow-up, but she was also small for dates. Just as in Group I, the only infants who did poorly at follow-up in Group III were the 2 who were small for dates (nos. 17 and 19). These 2 small-for-dates infants were close to term in gestational age, however, unlike the small-for-dates infants in Group I. This may indicate that the mechanism of intrauterine growth retardation in pre-eclampsia is different from that in other maternal diseases.

The only patient in Group III who had a precipitous drop in estriol excretion had a placental abruption, which may have been responsible, although the last estriol obtained was 14 days before delivery. The child (case no. 21) born two weeks after this drop, weighed 3070 gms. at birth and was perfectly normal on follow-up. However, since the estriol status immediately prior to delivery is unknown in case no. 21, it is difficult to relate the estriol pattern (? precipitously dropping) to later development, even though the child was normal on follow-up. In contrast, 3 of the 4 infants in this group born after chronically low estriols weighed less than 2000 gms. at birth, and 2 of the 3 did poorly on follow-up. The fourth child was large for dates because his mother was diabetic.

Very little can be said about the effect of maternal diseases here except that mothers with cyanotic heart disease are known to give rise to low birth weight babies (Cannell et al., 1963), and both mothers with tetralogy of fallot gave birth to babies weighing less than 2000 gms.

The results of this study agree in part with those found by other investigators. Although Greene et al. (1969) felt that low estriol excretion was compatible with normal development, only 1 of their 5 children whose mothers had pre-eclampsia weighed less than 2000 gms. at birth, and this child had seizures and fine motor problems on follow-up. In contrast, 4 children of pre-eclamptic mothers in this study were small for dates, and 5 children weighed less than 2000 gms. On follow-up 3 of the 4 small-for-dates infants were abnormal. One child was microcephalic with motor impairment, another had a seizure disorder and was retarded about one year developmentally, while another was hyperactive and retarded about eight months. The 2 other small-for-dates infants whose mothers had other pregnancy complications (nos. 17 and 19) were also abnormal. One child's head circumference was more than 2 S.D. below the mean, while the other probably had fine motor retardation. Six other children had minor physical defects but no clear relationship to either birth weight or estriol excretion was noted. Not enough of these congenital anomalies were present to evaluate Drillien's (1970) hypothesis that in children with congenital anomalies a primary developmental defect is responsible for both the disturbance in body and brain growth.

The tentative conclusion made from the patients in the present study, that babies born after precipitously dropping estriols do better than those babies born after chronically low estriols, agrees with the conclusion of Wallace and Michie (1966) that the longer the estriols are low, the more likely the child is to be retarded. In their pre-eclamptics

with chronically low estriols, the babies all weighed less than 1700 gms. and 2 of the 4 children had cerebral palsy at follow-up. In contrast, those pre-eclamptics with terminal falls in estriol excretion gave birth to 3 children who weighed 1900 gms.- 3000 gms. and did well. These results affirm the important clinical significance of precipitously dropping estriols as an indication for delivery since these children do very well. However, if estriols are chronically low and children are delivered for that reason, the children are unlikely to do well later in life.

Certain discrepancies in the data described here must be explained before presenting the conclusions. Except for case nos. 5 and 20, the relationship of estriol excretion and birth weight is as expected. The mother in case no. 20 was diabetic, and that explains the large birth weight of the baby. In case no. 5 the final estriol value in a series of chronically low values was 11.4, and this is the highest final value in the low estriol groups. Earlier, this patient had been hospitalized for an elective induction which failed. Perhaps fetal growth responded to this two week rest in the hospital, therapy known to increase utero-placental blood flow, while the estriol excretion, beginning its rise at this point, had not yet reflected the late fetal growth spurt that led to a normal weight infant. The reason why the child of case no. 4 is doing so well is difficult to explain. The mother had severe pre-eclampsia of long duration with chronically low estriols, while the child was delivered by Caesarean section at 35 weeks and was small for dates. Happily, although for unknown reasons (perhaps excellent nursing or maternal care or genetic factors), this child at 21 months is perfectly normal except for a minor anomaly of the foot.

V. SUMMARY AND CONCLUSIONS

A study of maternal estriol excretion and subsequent child development in 21 pregnancies is reported. Thirteen mothers (Groups I and III) had abnormally low estriol excretion patterns and 6 of their children were small for dates, while an additional 2 had birth weights less than 2500 gms. On follow-up examination, 5 of these children (all small for dates) had major problems in development or function such as microcephaly, seizure disorder, and developmental retardation with hyperactivity, while 3 had minor defects, 2 of which had birth weights less than 2000 gms. Both defects and severity were more related to chronically low estriols than precipitously dropping estriols, although minor defects also occurred in children whose mothers had normal estriol excretion. Eight mothers (Group II) had normal estriol excretions with pre-eclampsia, and all 8 children weighed more than 2500 gms. and were normal on follow-up, except for 3 children with minor embryological defects. In comparing Group I, pre-eclamptics with low estriols, with Group II, pre-eclamptics with normal estriols, the following additional conclusions were drawn:

1. Mothers who represent the extremes of age or who have poor obstetric histories are more likely to deliver small-for-dates babies who do poorly, and the low maternal urinary estriols reflect this feto-placental insufficiency.
2. Increased severity and duration of pre-eclampsia and superimposition on chronic hypertension are risk factors for low estriol excretion, and are indicative of a poor prognosis for the fetus; severe pre-eclampsia is more often associated with chronically low estriols, while mild pre-eclampsia is more often associated with precipitously dropping estriols.
3. Four of the 8 children in Group I (low urinary estriols with pre-eclampsia) were small for dates and of these, 3 had major neurological or developmental

defects on follow-up. The mothers of all 4 of these children had chronically low estriols. In contrast, none of the 4 children in the entire study whose mothers had precipitously dropping estriols were small for dates, and all were normal on follow-up. Three of the 4 had birth weights greater than 2500 gms.

4. All 8 children of mothers with normal estriol excretions had normal birth weights and did well on follow-up.

5. Only 1 of 4 children in the entire study with a birth weight under 1500 gms. was doing well at follow-up, while half of those whose birth weights were between 1500 and 2000 gms. were doing poorly.

Although abnormal estriol excretion patterns may be compatible with the development of normal children, in the cases studied here, children were more likely to be abnormal later in life if their mothers had chronically low levels of estriol excretion. Mothers with chronically low estriols tend to be older and to have more severe pre-eclampsia than mothers with normal or dropping estriols. Apparently, one of the most important factors for later healthy development is birth weight, and older mothers with more severe pre-eclampsia give birth to more small-for-dates infants who in turn are more likely to be abnormal. The chronically low estriols reflect both the infant's low birth weight and the severe pre-eclampsia, but the weight apparently is the predominating factor. Mothers with precipitously dropping estriols give birth to more normal weight infants who uniformly do well. If these infants are of appropriate gestational ages when the precipitous drop occurs, they should be delivered immediately. The data also suggest that if during pregnancy estriols are chronically low, early delivery salvages many infants who later develop gross neurological and developmental defects. If such infants are not gaining weight in utero, perhaps some method can be found such as intra-amniotic alimentation to treat the growth retardation in utero.

LITERATURE CITED

Aleem, F.A., et al., (1969): A method for oestriol estimation in amniotic fluid and its use in the study of normal and abnormal pregnancy. Steroids 13:651.

Bacola, E., et al., (1966): Perinatal and environmental factors in late neurogenic sequelae. Amer. J. Dis. Children 112:359.

Baird, D., et al., (1957): Birth weights and placental weights in pre-eclampsia. J. Obstet. Gynec. Brit. Cwlth.64:370.

Banerjea, S.K., et al., (1962): Index of placental function by endocrine assay and its clinical application in obstetrical practice. J. Obstet. Gynec. Brit. Cwlth 69:963.

Battaglia, F.C., et al., (1967): A practical classification of newborn infants by weight and gestational age. J. Ped. 71:159.

Beargie, R.A., et al., (1970): Growth and development of small-for-dates newborns. Ped. Clins. N. Amer. 17(1): 159.

Beischer, N.A., et al. (1968): The incidence and significance of low oestriol excretion in an obstetric population. J. Obstet. Gynaec. Brit. Cwlth. 75:1024.

Beling, C.G., (1963): Gel filtration of conjugated urinary oestrogens and its application in clinical assays. Acta Endo. Suppl. 79:82.

Beling, C.G., (1967): Estriol excretion in pregnancy and its application to clinical problems. In Advances in Obstetrics-Gynecology. Williams and Wilkins, Baltimore, p.88.

Berman, A., et al., (1968): Relationship of amniotic fluid estriol to maternal urinary estriol. Am. J. Obstet. Gynec. 100:15.

Brown, E.W., et al., (1946): Causes of prematurity. Amer. J. Dis. Children 71:378.

Buck, C., et al., (1969): The effect of single prenatal and natal complications upon the development of children of mature birthweight. Pediatrics 43:942.

Cannell, D.E., et al., (1963): Congenital heart disease and pregnancy. Am. J. Obstet. Gynec. 85:749.

Cohen, S.L., (1966): A method for the rapid colorimetric assay of total estrins in pregnancy urine. J. Clin. Endo. Metab. 26:994.

Cornblath, M., et al., (1959): Symptomatic neonatal hypoglycemia associated with toxemia of pregnancy. J. Ped. 55:545.

Creamer, B., (1955): Toxemia of pregnancy and the child. J. Obstet. Gynaec. Brit. Cwlth. 62:914.

Creasy, R.K., et al., (1972): Experimental intrauterine growth retardation in the sheep. Am. J. Obstet. Gynec. 112:566.

Diczfalusy, E., (1964): Endocrine functions of the human fetoplacental unit. Fed. Proc. 23:791.

Diczfalusy, E., et al., (1965). Steroid biogenesis and metabolism in the human foetoplacental unit at midpregnancy. Arch. d'Anat. Micro. 54:67.

Diczfalusy, E., (1969): Oestrogen metabolism in pregnancy. In Foetus and Placenta. ed. A. Klopper and E. Diczfalusy, Blackwell, Oxford, p. 191.

Drillien, C.M., (1961): A longitudinal study of the growth and development of prematurely and maturely born children. Arch. Dis. Childhood 36:241.

Drillien, C.M., (1964): The Growth and Development of the Prematurely Born Infant. Livingstone, Edinburgh.

Drillien, C.M., (1970): The small-for-date infant: etiology and prognosis. Ped. Clins. N. Amer. 17(1):9.

Eastman, N.J., et al., (1962): The obstetrical background of 753 cases of cerebral palsy. Obstet. Gynec. Survey 17:459.

Frandsen, U. and G. Stakemann, (1961): The site of production of oestrogenic hormones in human pregnancy. Acta Endo. 38:383.

Frankenburg, W.K., and J.B. Dodds, (1967): The Denver Developmental Screening Test. J. Ped.71:181.

Galbraith, R.S., (1970): Maternal urinary estriol excretion patterns in patients with chronic fetal insufficiency. Amer. J. Obstet. Gynec. 106:352.

Gant, N.F., et al., (1971): Study of the metabolic clearance rate of dehydroisoandrosterone sulfate in pregnancy. Am. J. Obstet. Gynec. 111:555.

Greene, J.W.Jr., et al., (1963): Urinary estriol as an index of placental function. Am. J. Obstet. Gynec. 85:1.

Greene, J.W. Jr., et al., (1965a): Placental function tests. Am. J. Obstet. Gynec. 92:1030.

Greene, J.W. Jr., et al., (1965b): The use of urinary estriol excretion in the management of pregnancies complicated by diabetes mellitus. Am. J. Obstet. Gynec. 91:684.

Greene, J.W. Jr., et al., (1969): Correlation of estriol excretion patterns of pregnant women with subsequent development of their children. Am. J. Obstet. Gynec. 105:730.

Greene, J.W. Jr., and R.A. Beargie, (1970): The use of urinary estriol excretion studies in the assessment of high-risk pregnancy. Ped. Clins. N.Amer. 17(1):43.

Gruenwald, P., (1963): Chronic fetal distress and placental insufficiency. Biol. Neonat. 5:215.

Gruenwald, P., (1965): Terminology of infants of low birth weight. Dev. Med. Child Neurol. 7:578.

Hausknecht, R.U., (1965): Maternal dehydroepiandrosterone and estrogen production in late pregnancy. Obst. and Gynec. 26:544.

Hausknecht, R.U., (1967): Estrogen production in a woman pregnant with an anencephalic fetus. Am. J. Obstet. Gynec. 97:1085.

Hellman, L., et al., (1971): Williams Obstetrics. Appleton Century Crofts, New York, pp. 178, 686.

Hughes, W.T., (1970): Infections and intrauterine growth retardation. Ped. Clins. N.Amer. 17(1):119.

Kawi, A.A., and B. Pas amanick, (1958): Association of factors of pregnancy with reading disorders in childhood. J.A.M.A. 166:1421.

Kellar, R., et al., (1959): Some clinical applications of oestrogen assay. J. Obstet. Gynaec. Brit. Emp.

Klopper, A., et al., (1963): Urinary excretion of estriol and pregnanediol during normal pregnancy. J. Obstet. Gynaec. Brit. Cwlth. 63:1024.

Klopper, A., (1968): The rise of estriol in the assessment of feto-placental function. Obstet. Gynec. Survey 23:813.

Klopper, A., (1969): The assessment of placental function in clinical practice. In Foetus and Placenta. ed. A. Klopper and E. Diczfalusy, Blackwell, Oxford, p.471.

Knobloch, H., et al., (1956): Neuropsychiatric sequelae of prematurity. J.A.M.A. 161:581.

Knobloch, H., et al., (1960): Enviornmental factors affecting human development before and after birth. Pediatrics 26:210.

Knobloch, H., et al., (1962): Mental subnormality. New Eng. J. Med. 266:1092.

Leffert, R.L., (1970): Urinary estrogens as a measure of fetoplacental well-being. Postgrad. Med. 47:51.

Lilienfeld, A., et al., (1951): A study of the association of factors of pregnancy and parturition with the development of cerebral palsy. Am. J. Hyg. 53:262.

Lilienfeld, A., et al., (1954): Association of maternal and fetal factors with the development of epilepsy. J.A.M.A. 155:719.

Lubchenco, L.O., et al., (1963): Sequelae of premature birth. Am. J. Dis. Children 106:101.

Lubchenco, L.O., et al., (1966): Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. Pediatrics 37:403.

Lubchenco, L.O., (1970): Assessment of gestational age and development at birth. Ped. Clins. N. Amer. 17(1): 125.

Maqueo, M., et al., (1964): Placental pathology in eclampsia and pre-eclampsia. Obst. and Gynec. 24:350.

Michie, E.A., (1967): Urinary oestriol excretion in pregnancies complicated by suspected retarded intrauterine growth, toxemia or essential hypertension. J. Obstet.Gynaec. Brit. Cwlth. 74:896.

Moghissi, K.S., et al., (1969): Relationships of maternal amino acid blood levels to fetal development. In Perinatal Factors Affecting Human Development. World Health Organization Scientific Publication No. 185:16.

Muller, P.F., et al., (1971): Perinatal factors and their relationship to mental retardation and other parameters of development. Am. J. Obstet. Gynec. 109:1205.

McDonald, A.D., (1962): Congenital defects associated with prematurity. Arch Dis. Childhood 37:277.

Naeye, R.L., (1966): Abnormalities in infants of mothers with toxemia of pregnancy. Am. J. Obstet. Gynec. 95:276.

Nellhaus, G., (1968): Head circumference from birth to 18 years. Pediatrics 41:106.

Nelson, W.E., et al., (1969): Textbook of Pediatrics. W.B. Saunders Co., Philadelphia p.p. 40-53.

Pasamanick, B., et al., (1955): Association of maternal and fetal factors with development of mental deficiency. J.A.M.A. 159:155.

Pasamanick, B., et al., (1956): Pregnancy experience and the development of behavior disorder in children. Am. J. Psych. 112:613.

Pasamanick, B., et al., (1960): Brain damage and reproductive casualty. Am. J. Orthopsych. 30:299.

Roy, E.J., et al., (1963): Concentration of oestrogens in blood and urine of patients suffering from pre-eclampsia. J. Obstet. Gynaec. Brit. Cwlth. 70:597.

Ryan, K.J., (1962): Hormones of the placenta. Am. J. Obstet. Gynec. 84:1695.

Schindler, A. and W.L. Herrmann, (1966): Estriol in pregnancy urine and amniotic fluid. Am. J. Obstet. Gynec. 95:301.

Scholz, B., et al., (1968): The physical and mental development of children of mothers with toxemia of pregnancy. Germ. Med. Mthly. 10:487.

Schulte, F.J., et al., (1971): Maternal toxemia, fetal malnutrition and motor behavior of the newborn. Pediatrics 48:871.

Sliteri, P.K., and P.C., MacDonald, (1966): Placental estrogen biosynthesis during human pregnancy. J. Clin. Endo. Metab. 26:751.

Stimmler, L., (1970): Infants who are small for gestational age. Proc. Roy. Soc. Med. 63:32.

Taylor, E.S., et al., (1963): Urinary estriol excretion of pregnant patients with pyelonephritis and Rh isoimmunization. Am. J. Obstet. Gynec.85:10.

Taylor, E.S., et al., (1965a): Estriol in pregnancy. Obst. and Gynec. 25:177.

Taylor, E.S., et al., (1965b): Estriol excretion in normal and complicated pregnancies. Clin. Obst. Gynec. 8:550.

Usher, R.H., (1970): Clinical and therapeutic aspects of fetal malnutrition. Ped. Clins. N. Amer. 18(1):169.

Van denBerg, B.J., and J. Yerushalmy, (1966): The relationship of the rate of intrauterine growth of infants of low birth weight to mortality, morbidity and congenital anomalies. J. Ped. 69:531.

Wallace, S.J., and E.A. Michie, (1966): A follow-up study of infants born to mothers with low oestriol excretion during pregnancy. Lancet 2:560.

Walker, J. (1965): Clinical obstetric features of prematurity and intrauterine growth retardation. Clin. Develop. Med. 19:36.

Yousem, H., et al., (1966): Maternal estriol excretion and fetal dysmaturity. Obst. and Gynec. 28:491.

YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

_____

_____

NAME AND ADDRESS DATE