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The use of ultrasonic estimated fetal weight in the diagnosis of intrauterine growth retardation

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Yale University School of Medicine
Yale - New Haven Hospital
Department of Obstetrics and Gynecology
1980

To

my Mother,

Phyllis, my wife

Elizabeth,
Rachel Hanna,
Ahuva Deborah,
Shoshana Mozelle,

Without their support, I could not have undertaken the challenge of medicine.

ACKNOWLEDGEMENTS

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Dr. Greggory R. DeVore, whose ideas were the seed of which this is the flower.

Ms. Marge Tortora, who taught me the ins and outs of ultrasonography.

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Dr. Daniel Freeman, who refreshed my knowledge of statistics.

Their contributions are like parts in a puzzle which must all be present for the whole picture to be meaningful; without them this thesis would not be complete.

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SECTION 1

INTRODUCTION

Since the early 1950's much concern has been expressed for infants whose birth weights have been less than expected based on their gestational age. The study of these infants, and more specifically their intrauterine course, gave rise to a myriad of terms describing these anomalies. The terms fetal microsomia, nanosomia, primordialis, and intrauterine dwarfism have given way in favor of the term intrauterine growth retardation (IUGR). It has been established that these infants have significantly higher perinatal mortality rates than normal infants and run the risk of developing neurological abnormalities later in life. It is, therefore, apparent that IUGR must be diagnosed as early as possible in order to remove the fetus from its apparently hostile environment or to institute whatever conservative therapy is available.

Over the course of years many methods have been devised to affect the diagnosis of IUGR. These range from the clinical judgment of the obstetrician, who uses external measurements and his clinical judgment to estimate fetal size appropriateness for gestational age; biochemical assays to measure the output of various hormones in the mother's urine; to the ultrasonic determination of the actual size

of various fetal parts and uterine dimensions. Since the former two are notorious for their inaccuracies, more and more weight is being given to the ultrasonically determined measurements. Foremost amongst these are the biparietal diameter, the total intrauterine volume, the head-to-body ratio and the estimated fetal weight. Previous studies at this institution have both designed and set the necessary control limits on the use of total intrauterine volume as a screening test for IUGR. Another study at this institution developed a system for estimating fetal weight using ultrasonically derived parameters. The control limits used in interpreting this weight were derived at another institution using the actual weights of infants at birth.

PURPOSE

This study is intended to develop the standard curve for ultrasonically estimated fetal weights at this institution so that the necessary control limits to diagnose IUGR based on this weight will be meaningful. An attempt will also be made to fit a mathematical expression to this curve using the appropriate mathematical methods. Once this is done the results can be compared to the existing tests (e.g., total intrauterine volume) to see whether they agree or diagree in the prediction of IUGR. In addition, we will see if these data are useful in pre-

dicting IUGR at birth and whether a model can be constructed which will predict eventual birth weight. Although the formula for estimated fetal weight was verified as part of the study which designed it, we will also attempt to reverify this formula using those points in our data base where birth was affected within 48 hours of an ultrasonic estimated fetal weight determination.

PART I

INTRAUTERINE GROWTH RETARDATION

SECTION 2

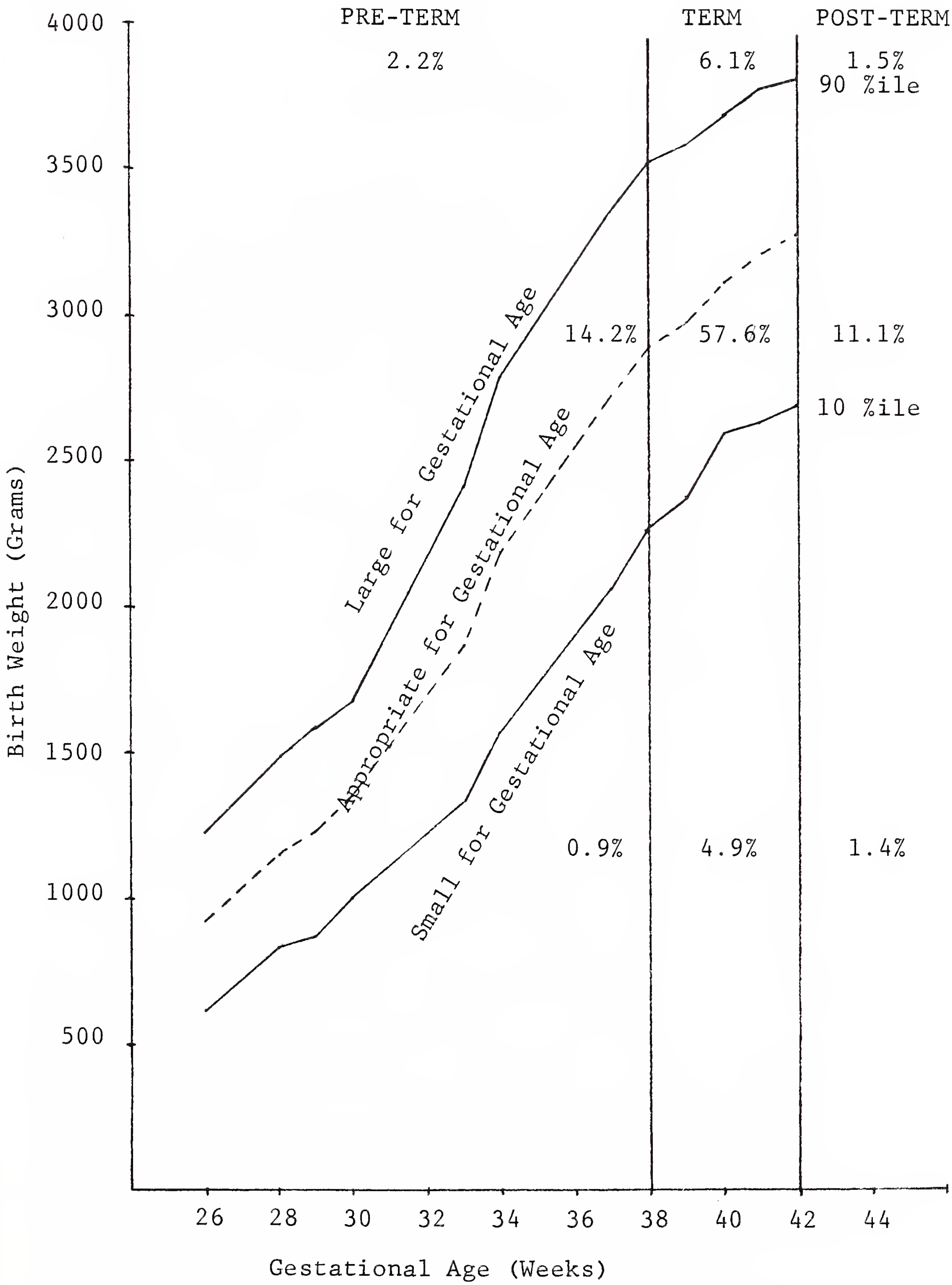
THE HISTORY OF IUGR

As early as 1902, Ballantyne described certain infants as having dry, parched skin, long nails, and a paucity of meconium-stained amniotic fluid, advanced ossofication for their premature weight and a markedly decreased quantity of subcutaneous fat. Because of this clear differentiation from a premature infant who, in spite of having the same birth weight, had a much different appearance, Ballantyne coined the term "dysmature" (3). In spite of this description made almost 80 years ago, until quite recently the term premature was used to describe an infant who weighed less than 2500 grams at birth without regard to its gestational age. In 1961, an expert committee of the World Health Organization suggested that newborn infants should not be classified as premature on the basis of weight alone (78). That same year, Warkany (74) coined the term intrauterine birth retardation (IUGR) to describe neonates that are within the tenth percentile of weight for gestational age. This term (IUGR) has become the currently accepted term for this condition.

The criteria for placing an infant in the IUGR category varies from author to author. Like Warkany, Battaglia and Lubchenco used the tenth percentile weight for gesta-

tional age as the cut off for calling a baby small for gestational age (7). Others, such as Usher and McLean used two standard deviations below the mean of birth weight as their definition (70). Using 1,617 neonates Lubchenco and her co-workers constructed what is now generally accepted as the standard curve for birth weight and gestational age (52). This graph can be divided vertically at 38 and 42 weeks into three sections. The area below 38 weeks is called pre-term, between 38 and 42 weeks term, and above 42 weeks post-term. It can be further subdivided along the vertical access by two sygmoidally shaped lines representing the 90th and 10th percentiles for weight at the respective gestational ages. The area above the 90th percentile is termed large for gestational age, between the 90th and 10th percentile appropriate for gestational age and below the 10th percentile small for gestational age. This is represented graphically in figure 1. The incidence of IUGR in the United States has been reported as being between 3 and 7% (12, 32). However, it must be born in mind that different authors use different criteria in assigning an infant to the IUGR category.

FIGURE 1



Standard Curve of Birth Weight by Gestational Age with Distribution of the Neonates (Curve according to Lubchenco (52), Distribution according to Bard (4))

SECTION 3

CAUSES OF IUGR

In order to discuss the causes of IUGR it is helpful to divide IUGR infants into two categories. Symetrical growth retardation is associated with both somatic and brain growth lag (40). Since this type of growth retardation occurs before the 28th week of gestation, it is seen in infants that have had some early insult. These include fetal infections (39, 47), genetic abnormalities (39, 44), and environmental insults including x-rays (2) and certain drugs such as heroin and alcohol (43). These infants seem to have a reduced cellular mass with a normal cellular size and are hence termed hypoplastic (15). Congenital anomalies are commonly seen in this group of infants. Asymetrical growth retardation is seen starting in the late second trimester. These infants are generally head-spared and are consequently born with a head size which is large in relation to body size. The etiologies generally include those which compromise the utero-placental blood flow (31). These include such environmental factors as high altitude and smoking (49, 55) and any maternal diseases which produce vascular insufficiency, such as toxemia or chronic hypertension and maternal anemias (39, 60). This late insult seems logical when one realises that this is the

period when the fetus is demanding more in the way of raw materials and energy sources to continue to maintain its growth rate. Since the major increase in cell number has taken place earlier in the pregnancy, these infants exhibit only a minimal decrease in cell number but a marked decrease in cell size (15). For this reason infants in this group are classified as hypotrophic.

SECTION 4

THE SEQUELAE OF IUGR

Approximately half of the IUGR babies have wasting of the soft tissue and muscle mass and marked diminishment of the subcutaneous adipose tissue. Body length and organ size is generally unaffected except in severe cases. The liver and thymus are exceptions to this rule and are generally decreased in size in the IUGR infant (4).

In the immediate postpartum period the IUGR infant has to cope with such problems as meconium aspiration, with secondary apneic episodes, pneumonitis, and pneumothoraxes (34). The neonate has problems with electrolyte and metabolic imbalances due either to intrapartum asphyxia or as a result of the chronic placental insufficiency. The metabolic acidosis caused by the intrapartum asphyxia can lead to compensatory respiratory alkalosis which in turn leads to cerebral edema and convulsions not uncommon in IUGR infants. The IUGR neonate also has difficulty maintaining body temperature, and hypoglycemia is reported in 27% of these infants with glucose levels dropping down to 30 mgs/100 ml (4, 5). This hypoglycemia can lead to central nervous system damage. The growth retarded baby may be plagued with polycythemia and thrombo-

cytopenia with the chance of a significant coagulopathy (34). Difficulties in maintaining blood calcium levels also may contribute to the tremors, convulsions and clonus. Overall, the British Perinatal Mortality Survey showed that IUGR babies born after 36 weeks of gestation exhibited a death rate during labor and the neonatal period which was eight times higher than for controlled babies of similar age with appropriate weight (13). Fitzhardinge and Steven found, in one set of follow-up studies of IUGR infants without major congenital anomolies, that growth rates, although rising substantially by six months, still continued to lag behind that of the general population (29). These same authors found that the IUGR infants had subsequent neurological deficits when compared against matched group of normals. Between 26 and 33 percent of the IUGR infants showed minimal to moderate speech defects compared against 1.5% in the control group. Visual defects range between 10 and 18% which was approximately double the control group figure. Almost one quarter were judged to be minimally brain damaged at age five compared with 1% for the control group (30). Vohr, et al, tested pre-term small for gestational age infants using such tests as the Bayley score of infant development (72). They showed that the IUGR infants had significantly lower scores during the first eighteen months of life but had caught up by twenty

four months of age. In that study the age for the preterm infants was adjusted downward by the number of weeks less than term when the baby was born.

SECTION 5

DIAGNOSING IUGR

CLINICAL DIAGNOSIS

Over the years the clinician has used various external measurements, patient history and predisposing factors, in combination with his clinical judgment to arrive at a decision on the adequacy of fetal growth.

Maternal History

The physician could first be concerned that the fetus might be growth retarded based on the patient's history which may or may not show any of the predisposing factors previously listed in the section of IUGR causes.

Fundal Height

Traditionally, the height of the top of the fundus measured from the symphysis pubis in the midline has been related to the gestational age. The generally accepted formula is that height in centimeters is equal to gestational age in weeks up to 38 weeks, with a possible slight drop thereafter. A physician might therefore, become alarmed if either the fundal height appeared small for the calculated gestational age or if the examination to examination increase in fundal height failed to mater-

ialize. While Beazley, in his study, found fundal height to be essentially useless (8), Belizan, et al, developed a workable nomogram (10). In this recent study, the fundal heights were quantified by gestational age with appropriate measurements indicating the 90th and 10th percentiles. Of those patients who were above the 10th percentile 14% had IUGR babies; of those who fell below the 10th percentile and were, therefore, suspected of have IUGR only 10% did not.

Maternal Weight Gain

Another warning flag used by physicians is the maternal weight gain. Since a woman can be expected to gain approximately 20 pounds over pregnancy, a weight gain per week which is inadequate to achieve this overall gain or, more importantly, if there is inadequate examination to examination weight gain in the third trimester, makes the physician suspect IUGR (2, 14).

Estimation of Fetal Weight by Palpation

Judgment of the fetal weight by palpation is probably the least accurate of the methods. Loeffler showed that these estimations were accurate to within 458 grams in 80% of the cases, however, the accuracy dropped to 43% when the fetus in fact weighed less than 2,270 grams (50).

Unfortunately, it is precisely these infants which are of the most concerned.

Studies designed to show the efficacy of these methods for diagnosing IUGR showed the prediction rate ranging between 29 and 52% (16, 51, 56). The bottom line therefore on clinical judgment must be that it can be used as a screening tool, using a wide margin of suspicion, so that hopefully less IUGR babies will slip through the net, and will get funnelled on to appropriate diagnostic methods listed below.

BIO-ASSAYS IN THE DIAGNOSIS OF IUGR

Human Placental Lactogen

Spellacy reported that human placental lactogen may be helpful in the diagnosis of IUGR. Since one of the causes of IUGR may be a small placenta which compromises the placental blood flow, one would expect that such a placenta would produce lower levels of HPL (65). Unfortunately, this is not the only cause of IUGR, and IUGR babies with normal size placentas would not be expected to exhibit low HPL levels. In two different studies five out of fifteen patients and two out of twelve patients with IUGR exhibited low levels of HPL (45, 69). It should therefore be obvious that human placental latrogen

is probably not a useful test for screening for IUGR.

Estriol Excretion

Estriol is created by the maternal fetal unit and, therefore, is generally considered to correlate well with fetal size (11, 26, 46, 57). In fact, estriol excretion in the maternal urine does tend to be depressed when fetal growth is retarded. However, individual variation overlaps enough to make only gross judgments from a single measurement. Many authors cite figures that show fairly unacceptable false positive and false negative percentages using estriol excretion (9, 27, 33, 46, 58, 69, 78). Campbell even found that the biparietal diameter was a better predictor of birth weight than the estriol determination (18), and as we shall see below the biparietal diameter is not one of the better predictors of birth weight among the ultrasonic measurements.

It has been noted however that within one individual serial measurements of urinary estriol excretion can be useful. Weekly samples of 24 hour urine estriol determinations should show a significant week to week increase. No increase, or worse a decrease, usually signifies a fetus that is stressed. Obviously, the collection of weekly 24 hour urines for estriol determinations cannot be used as a screening tool for all women and must be reserved for

those in the at-risk category or those suspected of having an IUGR baby. Tulchinsky does, however, propose screening with two estriol determinations, one between 32 and 33 weeks and another between 35 and 37 weeks (68). Of the patients in this test group with subnormal estriol excretion 21% were found to have IUGR, 35% developed hypertensive disease of pregnancy, and 31% were found to have severe anemia. The false negative rate in this study was only 3.1%.

BIOELECTRIC METHODS

The development of fetal heart rate and contraction monitors over the last two decades was originally designed as an aid to physicians of patients in the intrapartum period. These machines were originally designed with internal monitors which required some dilation of the cervix and rupture of the fetal membranes. The advent of external monitoring utilizing ultrasound and the Doppler principle to measure fetal heartrate and tocodynametry to measure uterine contractions have lead to the utilization of this tool in the evaluation of fetuses in the antepartum period. The basis of this test is that during a uterine contraction there is an intermittant decrease in the intervillous space blood flow and the radial arteries which traverse the myometrium are compressed. These lead to a decrease in the amount of oxygen available and trans-

ferred from the mother to the fetus during the contraction. Under normal circumstances this reduced blood flow is transient and is tolerated well by the fetus. However, if the uterine blood flow was originally diminished and if the fetal reserve is already marginal this diminution in oxygen availability will cause a rapid deterioration in status of the fetus. This may be exhibited by seeing late decelerations during and after a contraction, by fetal bradycardia and tachycardia, and by reduced beat-to-beat variability of the fetal heart rate. This test may be conducted in two different ways. This first is the Non-Stress Test where monitoring is done with no other interference and second the Oxytocin Challenge Test in which oxytocin is administered intravenously until a stress of three contractions lasting at least forty seconds each during a ten minute period is experienced. This test has been used extensively by many physicians (20, 28, 59, 64). If it is believed that the fetus is at risk, weekly testing must be done. It has been shown statistically that the fetus is at a very small risk of intrauterine demise during the week following a negative test (19, 59).

ULTRASONIC DIAGNOSIS

Basic Measurements

In evaluating a fetus by ultrasonography, certain measurements are made directly and others are derived. The biparietal diameter is the diameter of the fetal skull measured at the level of the thalami at right angles to the falx cerebri and is shown in Figure 2. It is used directly, as a measure of gestational age and in the computation of the estimated fetal weight. The longitudinal diameter of the uterus is the largest longitudinal dimension between the level of the internal cervical os and the top of the fundus seen on a sagital scan. In this same scan the widest distance between the anterior and posterior walls of the uterus perpendicular to the longitudinal measurement is called the anteroposterior diameter. These two are shown in Figure 3a. A transverse scan of the uterus is then done at right angles to the longitudinal measurement at the level of the largest anteroposterior diameter. The measurement between the side walls is called the transverse diameter. This diameter, plus again the anteroposterior diameter may be seen in Figure 3b. These figures are used in the calculation of total intrauterine volume. A transverse section through the fetal skull, again at the level of the thalami, and a transverse section through the fetal abdomen at the level of the insertion of the umbilical cord give respectively the head and abdominal circumferences. These may be seen in Figure 4. The head circumference is used in the head-to-body ratio

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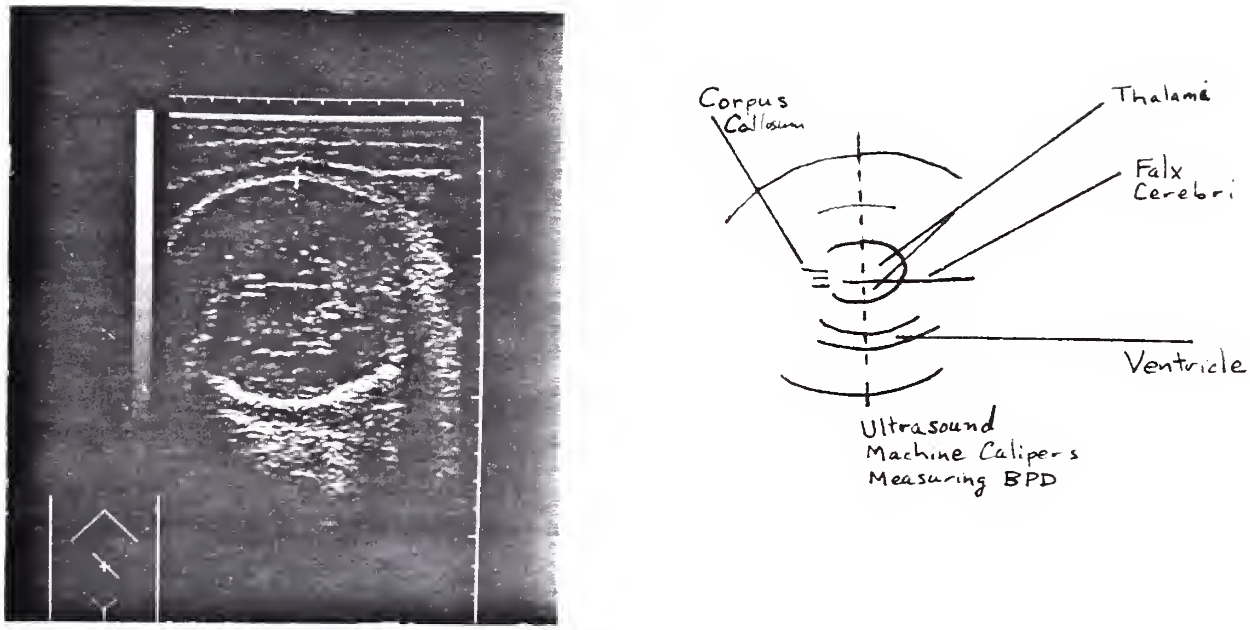
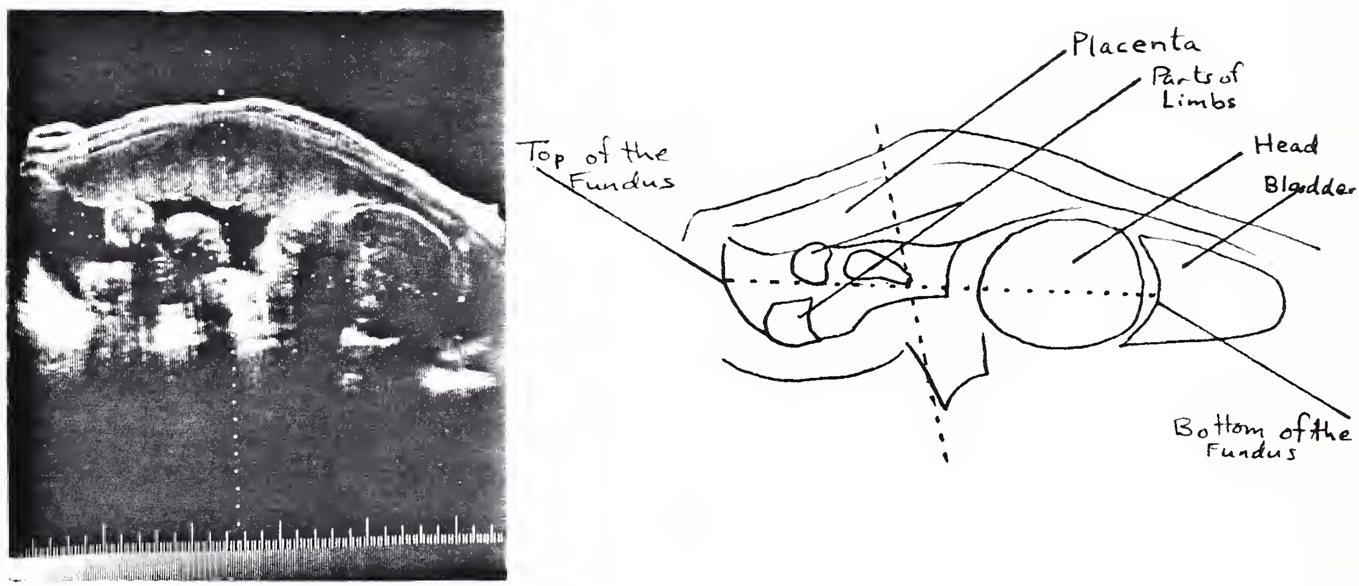
the top of

Figure 2

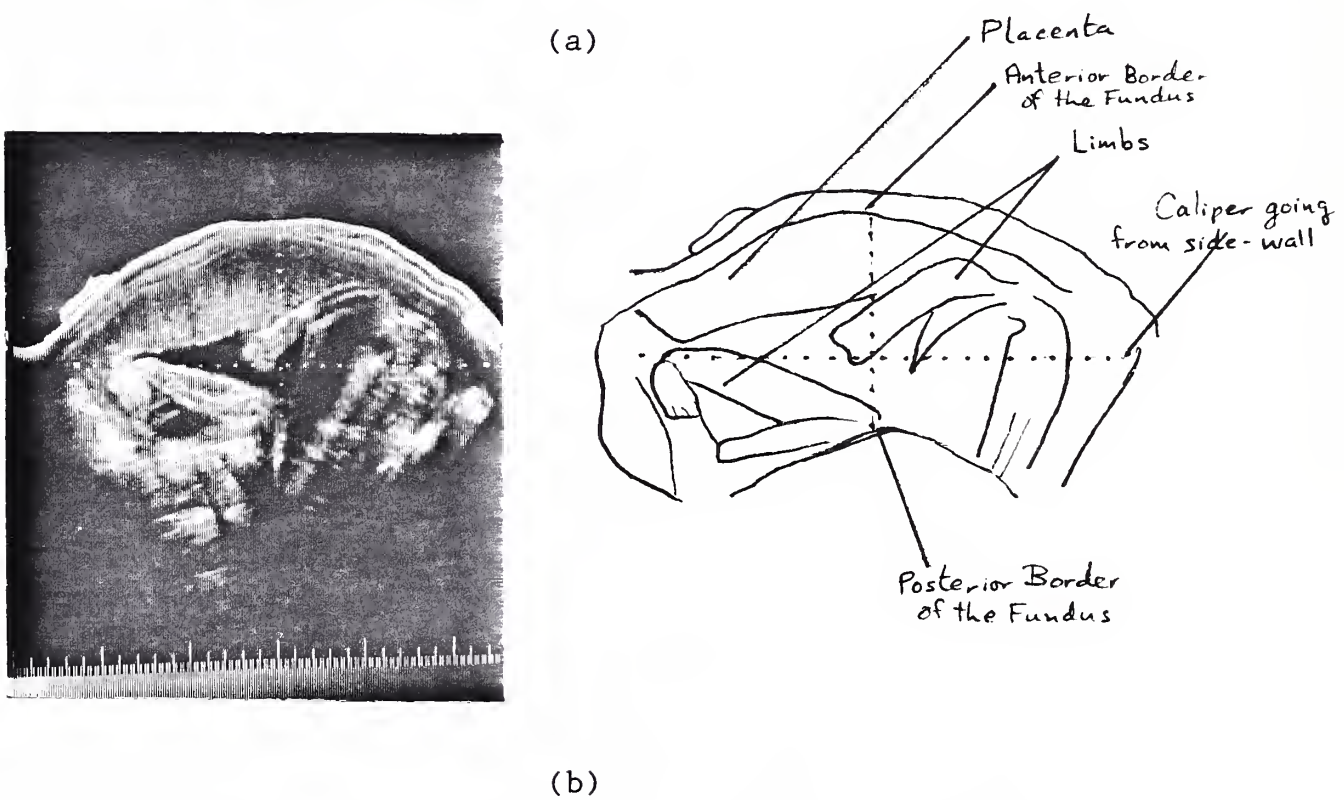


B - Scan ultrasonograph of the fetal skull at the level of the thalami showing measurement of the biparietal diameter.

Figure 3



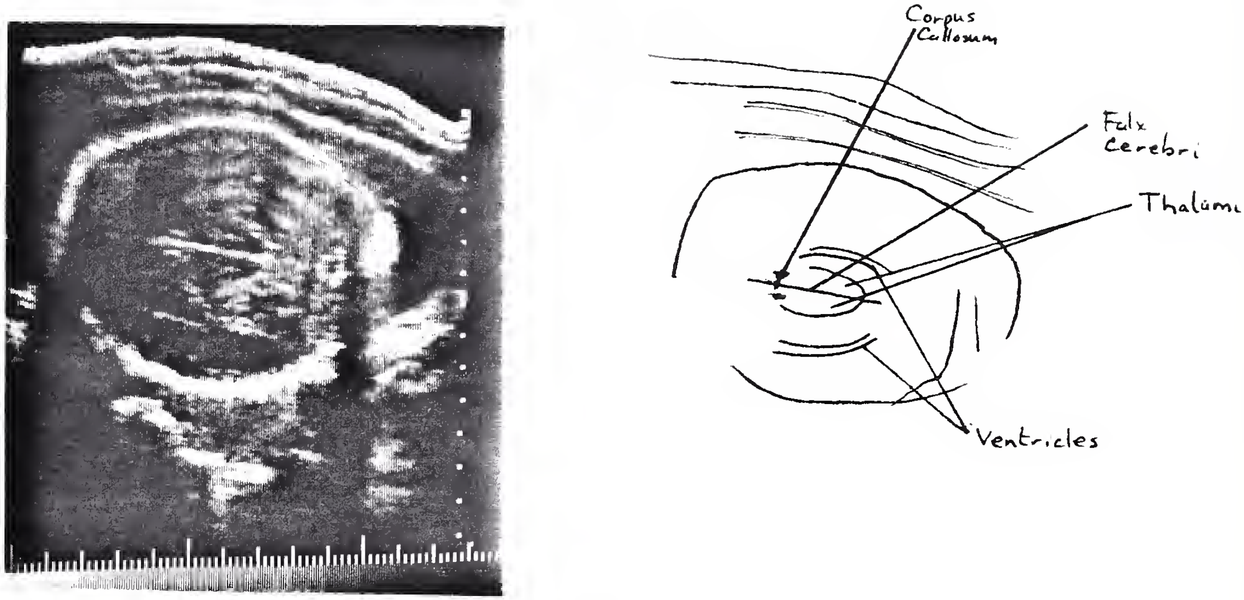
(a)



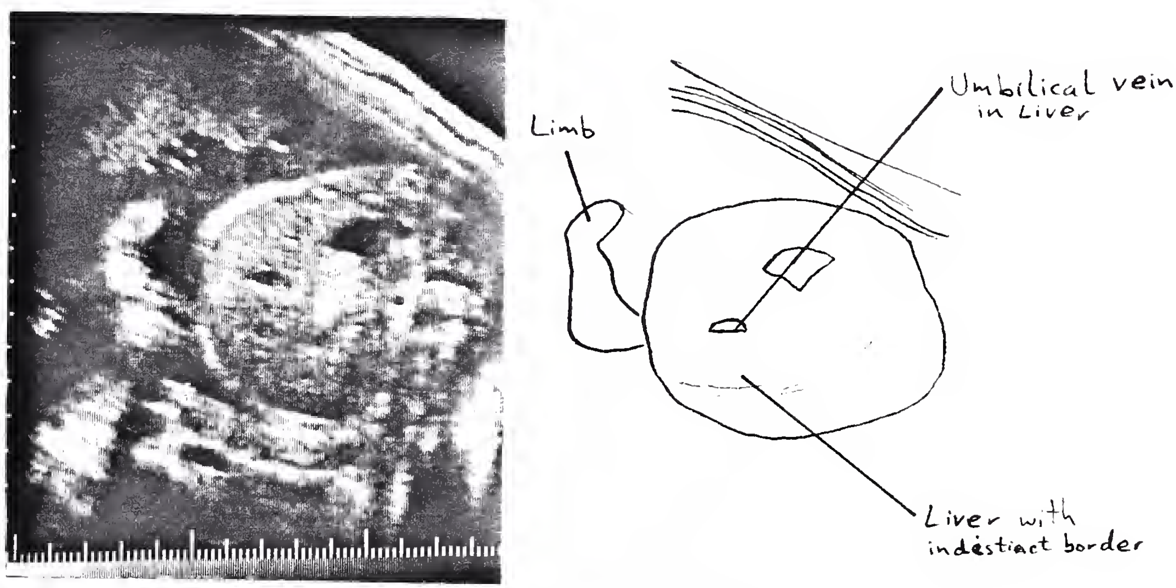
(b)

Gray-scale ultrasonograph of a sagital section in the mid-line (a) and transverse section at the level of the greatest anteroposterior diameter (b). Used to find the three uterine dimensions.

Figure 4



(a)



(b)

Gray-scale ultrasonographs of a cross-section of the fetal head at the level of the thalami (a); and a cross-section of the fetal abdomen at the level of the insertion of the umbilical cord (b). Used to measure head and abdominal circumferences.

and the abdominal circumference is used both in the calculation of estimated fetal weight and the head-to-body ratio.

Biparietal Diameter

The measurement of the biparietal diameter as an indicator of intrauterine growth retardation is subject to the following errors. In symetrical IUGR, the biparietal diameter will indeed be small for dates. However, taken alone there can be much confusion over which date is correct; that derived from the reported last menstrual period or that derived from the biparietal diameter. This is confounded when the woman is not sure of her dates or has had irregular periods. In asymetrical growth retardation, the biparietal diameter will in fact parallel gestational age computed by dates, since in this form of growth retardation there is head sparing (21).

Other authors have reported following serial BPD's and arriving at a rate of change of BPD per week (1, 22, 62, 63). However, this method which essentially measures the slope of the curve biparietal diameter versus weeks of gestation, must be accurate enough to detect changes as the slope approaches its lowest values. Late in gestation this slope is approximately 1.4 mm per week. If the standard error of the measurement is 2 mm, then with

95% confidence (or +/- 2 standard deviations) this would be equivalent to approximately 3 weeks, making interpretation meaningless. In addition, it must be noted that certain diabetic women have macrosomic infants which, in some ways, may be considered the exact opposite of an IUGR infant, and would have the same BPD with a much larger body.

Total Intrauterine Volume

The total intrauterine volume is a figure which should reflect overall fetal growth. This number should take in the increase of all fetal parts including the fetus itself, the placenta and the amniotic fluid (which is produced by the fetal system). If one assumes that the uterine cavity is in fact an ellipse its volume may be computed from the longitudinal, transverse and anteroposterior diameters using the geometrical formula for the volume of an ellipse:

$$V = \frac{4}{3} \pi \left(\tfrac{1}{2} L \times \tfrac{1}{2} H \times \tfrac{1}{2} AP\right)$$

After summing all the constants, this can be reduced to:

$$V = 0.5233 \times L \times H \times AP$$

In 1977 Gohari, Berkowitz and Hobbins at this institution, reported the results of the use of total intrauterine volume as a screening test for intrauterine growth retardation (35). Based on their results, a nomogram was constructed and critical values were set as follows: down

to one standard deviation below the mean is called the normal area; between 1 and 1½ standard deviations below the mean is termed the gray zone; below 1½ standard deviations below the mean is called the abnormal area. Over the course of the four plus years during which this measurement has been used at this institution there have been an approximately 25% false positive rate (21). It is felt that these false positives were due to normal fetuses who were genetically small and hence fell on the tail of the Gaussian distribution, but were in fact normal and those infants whose total intrauterine volume was decreased because of oligohydramnios of a non-IUGR cause. In fact, if a woman has a normal examination IUGR is generally excluded. If the examination is either abnormal or in the gray zone, other values mentioned below are also computed and, in addition, a repeat scan is usually scheduled for between 2 and 3 weeks. If on the repeat scan the woman appears to have tracked properly up a parallel curve then it is assumed that either she has a normal small infant or that her dating by last menstrual period is, in fact, off.

Head-to-Body Ratio

The head-to-body ratio is an extremely useful tool when evaluating asymetrical growth retardation. Early in pregnancy, at about 13 weeks, the head-to-body ratio

is about 1.3. As pregnancy progresses the body starts to catch up with the head and at term this ratio is essentially unity (17). In a growth retarded fetus, this eventual equality between head and abdominal circumferences is not realized. It has been reported that in 71% of the cases of IUGR the head to body ratio was above the 95th percentile for gestation.

Estimated Fetal Weight

For years investigators have attempted to assess fetal weight using actual measurements of various fetal parts. Early investigators used fetal head dimensions including the biparietal diameter, the occiptofrontal diameter, head circumference and head area to predict fetal weight (6, 16, 38, 42, 48, 66, 71, 76). Not surprisingly, the results of these studies were generally disappointing, having standard deviations ranging from 350 grams on up. In view of the previous discussion noting a particular head size with both IUGR and macrosomic infants, this result was to be expected. Later, researchers entered the measurement of other fetal body parameters to the formulae, notably chest diameters and skull and chest area measurement (37, 53, 66, 67). These studies reduced the standard error into the 200 gram range. In 1977, at this institution, Warsof, et al reported a method which utilized computer-assisted analysis of data to derive the best formula for fetal weight from

the three independent variables biparietal diameter, abdominal circumference and total intrauterine volume (75). The best fit was obtained by correlating the log of the birth weight with abdominal circumference and biparietal diameter. Using this formula, fetal weights could be estimated to within +/- 106 gm/kg. In addition, most of the other methods mentioned above were not accurate at the lower birth weights which is precisely where the most accuracy is needed. The formula derived here is accurate at both ends of the scale. This formula was subsequently checked out in a prospective study. It will be reverified using the data derived during this study.

PART II

A BRIEF DESCRIPTION OF ULTRASOUND

SECTION 6

THE BACKGROUND OF ULTRASOUND

HISTORY

Ultrasound is a fairly new tool in medicine having been introduced less than 25 years ago. The idea of using a mechanical or an electromagnetic wave to detect an unseen object began before World War II with the development of sonar. At that time it was discovered that a sound wave beamed into the water would bounce back and could be picked up by a receiver, and with the knowledge of the direction of reception and the elapsed time between transmission and reception, a location could be given to this object. The strength of the return signal gave some indication of the size and composition of the object in question. Naturally a submarine, which is a fairly large object made of metal, would give a nice return and, hence, could be detected by a surface vessel. Most of the frequencies used in sonar were in the range of sound that is audible to the human ear. Later, during World War II radar was developed where electromagnetic waves could be sent into the air and, by the same principle of reflection, reception at a given angle, and elapsed time, a position for the unseen object, in this case presumably an aircraft, could be determined. In the case of radar a system of pulsed transmissions was

used, the great majority of the station's time being utilized in receiving. This concept is also used in clinical ultrasound as will be seen below.

THEORY

In 1880, the Curie brothers noted that when mechanical energy was applied to certain quartz crystals a voltage was created across the crystal. Conversely, if a voltage is applied across the crystal a mechanical vibration would be set up. These affects are known as the piezoelectric and reverse piezoelectric effects respectively. In obstetrical ultrasound, a crystal is used which produces a sound wave from between 2-5 MHz with a transmitting time of approximately 0.1%; the remainder of the time the same crystal receives the return from the object being scanned. The cycling time with most obstetrical ultrasound machines is approximately 1,000 Hz; this means that the crystal will be transmitting receiving and back to the start of the transmission again in 1/1000 of a second. Since the transmission time is 0.1% or 1/1000, the actual time of a pulse is approximately 1/1,000,000 of a second.

The first method of representation of this ultrasonic information was the A-mode, which stood for amplitude modulation. In this method a spike would appear vertically with a given amplitude, proportional to the strength of the

returned signal along a horizontal axis representing the elapsed time and hence distance to the object. Since sound energy is rapidly absorbed as it passes through tissues the waves reflected from deeper in the object under investigation, in this case a human body, would be attenuated. To compensate for this a time compensated gain was added; as the time of the return lengthened a multiplication factor was added so that their amplitudes would be meaningful. The second mode of operation was M-mode or motion mode. In this mode, the horizontal axis from the A-mode was placed across a moving strip of paper as a series of marks. This allowed the recording of a moving object within the body, such as heart walls and valves. B-mode, or brightness mode, allowed A-mode to go into two dimensions. Since the amplitude would have to have to come out of the screen toward the viewer (which is impossible), the amplitude is translated into the brightness of the dot on the screen. The final modification is changing the sharp edge of the brightness B-mode to various shades of black, white and gray known as gray-scale to represent the amplitude of the return signal. Both B-scan and gray-scale, as described above, have one crystal transducer and, consequently, as this is moved around to various locations, always sensed by the machine, it paints one still picture on the screen. Real-time machines in contrast have many

transducers lined up in a row and consequently are scanning a whole slice at a time which is constantly changing on the screen. This allows one to observe movement of the object, in this case the fetus.

SECTION 7

ULTRASOUND IN OBSTETRICS

EFFECTS OF ULTRASOUND

It has been shown by some researchers that ultrasound may have certain deleterious affects when used in intensities of greater than 50 Watts/sq. cm., however, there have been no reports of permanent biological damage with intensities less than 10 Watts/sq. cm. (36). The energy used in clinical ultrasound ranges between 0.001-0.050 Watts per sq. cm. All studies to date seem to indicate that no damage is done either to the mother or the fetus at these intensities (54, 61, 77). The abdominal and, more specifically, obstetrical use of ultrasound was advocated by Donald as early as 1958 (23-25). In addition to being safer than x-rays or nuclear scanning, one achieves much finer differentiation of the soft tissues, which is exactly what is required in dealing with obstetrics. In fact the only real preparation needed for the scan is a full bladder which lifts the uterus out of the pelvis and pushes any air filled loops of bowel out of the path of the ultrasonic beam.

USES OF ULTRASOUND

Ultrasound can be used from almost the beginning of

pregnancy. We have recently noted the beginning gestational sack as early as the fourth week of gestation, that is to say two weeks after conception or approximately the time of the first missed period. This is approximately 9 days before the first urinary pregnancy test would appear positive.

In the experience of this institution, ultrasound has been used for the accurate diagnosis of many fetal anomolies including spina bifida, urachal cyst, ovarian cyst, and duodenal atresia. In addition the location of the placenta can be determined to rule out placenta previa and recent studies here by Hobbins, et al, have demonstrated that maturity can be diagnosed by examining the ultrasonic texture of the placenta (41).

As outlined in the previous sections ultrasound can be used to measure various fetal dimensions which can then be translated into gestational age for dating, and total intrauterine volume, head-to-body ratio and estimated fetal weight for the diagnosis of intrauterine growth retardation. To do this with a reasonable degree of accuracy requires the proper formulas for calculating these derived parameters, and nomograms which can be used as yardsticks with which to measure them. The formulas for these parameters have been previously derived (35, 17, 75), as have the nomograms for total intrauterine volume (35) and head-to-body ratio (17). There has been no similar nomogram against which to evaluate estimated

fetal weight; a curve of true birth weight is used instead (52). One of the goals of this project is to derive this nomogram. In addition, the ability to predict eventual birth weight, based on these parameters, would be of obvious value.

In this light, we have evaluated the results of 1281 ultrasound scans of 889 women seen at the Perinatal Unit at this institution during the last two years. The details of this evaluation and the models, nomograms and conclusions reached, will be found in the following part "The Experimental Analysis".

PART III

THE EXPERIMENTAL ANALYSIS

SECTION 8

MATERIALS AND METHODS

MEASUREMENTS

In the perinatal unit of the Yale New Haven Hospital, referred outpatients are routinely ultrasounded using a Picker Electronics ultrasonograph with a gray-scale converter. The biparietal diameter is measured using the internal electronic calipers of the ultrasonograph. Measurements of uterine dimensions for calculation of the total intrauterine volume is either made by measuring the dimensions off polaroid photographs of the ultrasonograph screen with the appropriate scale or using the internal measuring device of the machine. Head circumference and abdominal circumference were measured off the polaroid photographs using a standard map reader and applying the appropriate conversion scale.

THE DATA BASE

Subject Selection

In order to properly evaluate the results, the bias introduced by the selection of the patients must be considered. First, and foremost, the patients that are ultrasounded at the perinatal unit are those referred there

by different physicians in a number of ways. Clinic patients from the Yale New Haven Hospital who have questionable dates or suspected IUGR are generally first sent to the standard abdominal ultrasound unit where routine ultrasounds are performed for dating. In the event there are any problems they are then referred to the perinatal unit. Patients of the Yale New Haven Hospital high-risk obstetrical clinic, which includes patients at-risk for IUGR, diabetics, etc. are routinely scanned in the perinatal unit. Referrals also come from the private attending staff of the Yale New Haven Hospital where there is a suspicion of IUGR, diabetes, or other risk factor. In addition, as a tertiary care center the perinatal unit at the Yale New Haven Hospital receives referrals from a catchment area going from New Haven, Connecticut east to New London, Connecticut, west to the Bridgeport and environs area, north towards the Hartford area and northwest as far as Poughkepsie, New York.

Although this population is probably biased towards the problem cases, nevertheless there are a great many women for whom the ultrasonic diagnosis is completely negative. The group being studied consists of all the women who, during the course of their ultrasounds, had at least one set of measurements taken among which were the figures necessary to do an estimated fetal weight. All women who

received such scans during the years 1978 and 1979 were considered. This group consisted of 889 women and comprised a total of 1,281 data points.

Data Recorded

In addition to the estimated fetal weight the following data were also recorded: the total intrauterine volume, the head-to-body ratio, the date of the examination, the gestational age as determined by the biparietal diameter, some form of information relating to the last menstrual period of the patient, the gestational age at the first ultrasound done at our institution (whether or not an estimated fetal weight was done at that time), and the birth date and weight of the infant if available.

Further Selection

Since all parameters depended on accurate gestational ages, the women were divided up into four groups as follows: group I included those women for whom no dating history could be obtained, and in addition their first ultrasound indicated a gestational age of greater than 28 weeks which was considered sufficiently inaccurate, when used as an unconfirmed figure, to be considered worthwhile. Group II consisted of those women who claimed to know the date of their last menstrual period but for whom their

first ultrasound showed a date greater than 28 weeks which differed from their gestational age by dates by more than 1½ weeks; it is assumed in this instance that neither date could be considered reliable. Group III consisted of those women who claim to know the date of their last menstrual period and who on first ultrasound had a gestational age by ultrasound of greater than 28 weeks but for whom the gestational age by dates and ultrasound matched within 1½ weeks; the women's gestational age by dates was then assumed to be correct. Group IV consisted of those women who on first ultrasound had a gestational age of less than 28 weeks which was considered to be accurate enough for use regardless of the women's dating. This may be seen in Table 1. After the first computer pass, all data points in groups I and II were rejected. This left a data base with 830 data points.

For those formulae which use eventual birth weight of the infant as a dependant variable the data base had to be further selected down to those for which a birth weight was available. This group comprised 398 women and 635 data points. Obviously, to avoid auto-correlation only one data point per woman could be used to determine the model. Trials were made using the first or only data point for each woman and last or only data point for each woman and these both gave similar results. Therefore, the results presented here are those for the first or only

TABLE 1

DEFINITION OF GROUPS

Group	Description	Date Used
I	No LMP; First U/S age > 28 weeks	First U/S
II	LMP dates differ from First U/S age by > 1.5 weeks First U/S age > 28 weeks	LMP
III	LMP dates agree with First U/S age difference ≤ 1.5 weeks First U/S age > 28 weeks	LMP
IV	First U/S age ≤ 28 weeks regardless of LMP	First U/S

data point per woman. In addition, in the section on confirmation of the estimated fetal weight formula the entire group of 889 women was used since dating was not a problem; the only criteria was that the birth was affected within 48 hours of the ultrasound reading. There was only a subset of 80 women which fell into this category.

DATA MANIPULATION

Data Processing

The data processing and selection programs plus the programs to determine simple statistics were written by this author; the crosstabulation and regressions were done using the Statistical Package for the Social Sciences release 8.0. The processing was done at the Yale University Computer Center using an IBM 370/158.

Assumptions

In order to crosstabulate the various parameters, certain criteria were used to assign a value to a "coded" category (e.g., OK or IUGR). This criteria are:

1. Birth Weight: the infant is assigned to the IUGR category if its birth weight is less than the 10th percentile for gestational age, based on the summary statistics in Table 4. Student's

t probability was used to calculate the 10th percentile. Some week-classes were lumped together if there were insufficient cases in a class. Interpolation was done for non-whole-week figures. Since the infants came from this population, it was felt fair to judge them using this criteria.

2. Estimated Fetal Weight: the fetus is assigned to the IUGR category if its estimated weight is less than the 10th percentile for gestational age. Two methods were used; both are reported. Method 1 uses the summary statistics in Table 2 in an identical fashion to that for Birth Weight (above). Method 2 uses the best generated formula's Standard Error multiplied by -1.28 (lower 10th percent Z-score by Gaussian distribution).

3. Total Intrauterine Volume: the fetus is assigned to the gray-zone or IUGR category if the TIUV is below 1.0 or 1.5 standard deviations below the mean for gestational age respectively. This is based on the original data from Gohari, et al (35).

4. Head-to-Body Ratio: the fetus is assigned to the IUGR category if the ratio is above the 95th percentile for gestational age based on the reported data from Campbell (17).

The Z-scores for Estimated Fetal Weights were calculated using the same two methods as for "coding" in #2 above.

SECTION 9

RESULTS

SUMMARY STATISTICS OF EFW

The estimated fetal weights for all 830 observations in Groups III and IV were evaluated by gestational-age-in-weeks classes. The gestational age for the particular observation was rounded to the nearest number of weeks to determine the class. The mean and standard deviation for estimated fetal weight by class was calculated and these along with the number of observations per class are reported in Table 2. It will be noted that the lowest observation was at 15 weeks and 134 grams; the highest observation was at 43 weeks with a mean of 3,970 grams. The classes below 21 weeks and above 40 weeks exhibit a paucity of observations, and must, therefore, be used with caution. In the coding of estimated fetal weight above and below the 10th percentile based on this table, the classes at the high and low end were summed together with their respective neighbors to make the class means and standard deviations more meaningful. The 10th percentile level has been calculated by multiplying the standard deviation by the appropriate t statistic for a 10th percent tail based on the number of cases in the class and subtracting this from the mean. The statistics shown in Table 2 are represented graphically in Figure 5a.

TABLE 2

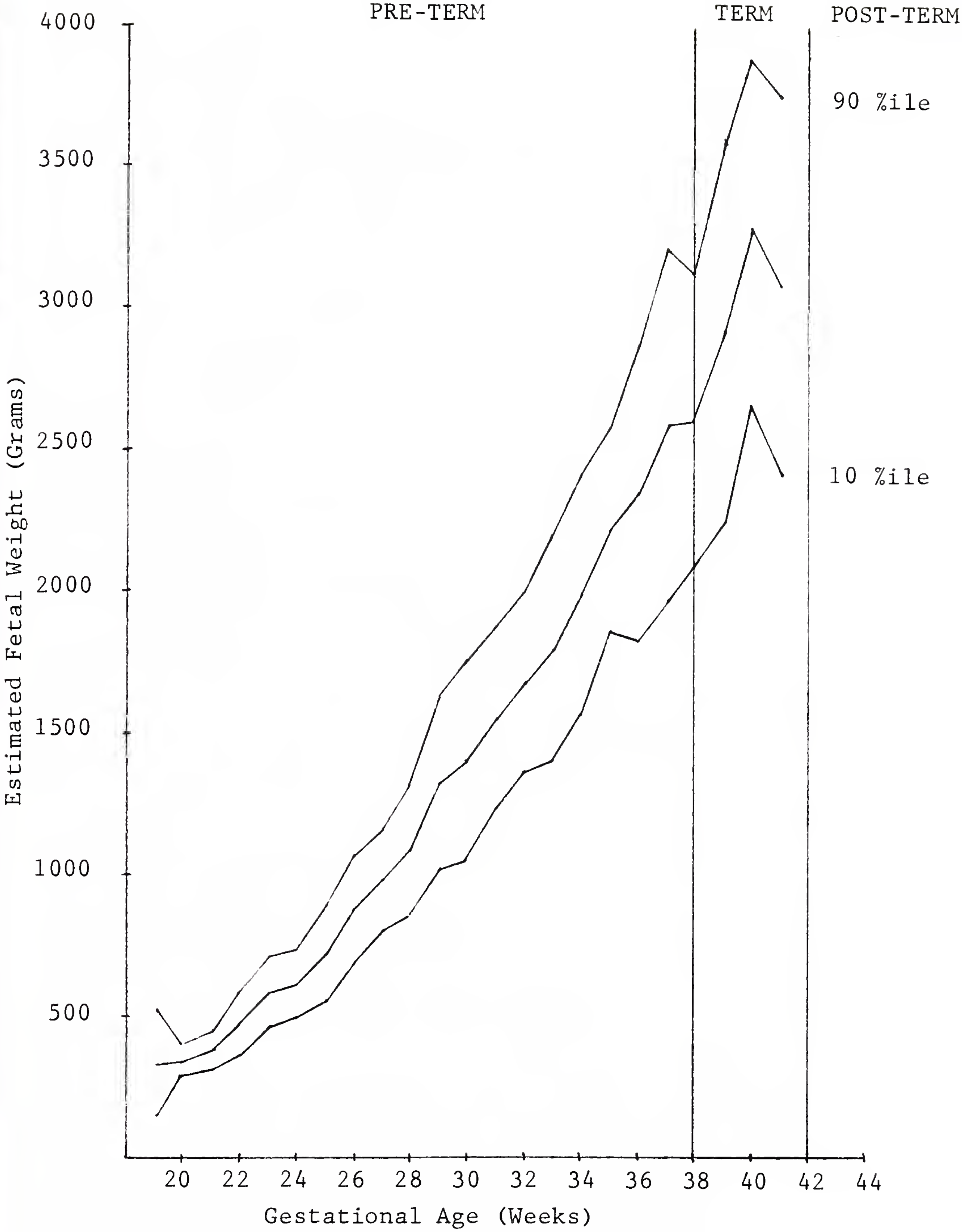
Summary Statistics of Estimated Fetal Weight

by Observation in Groups III and IV

(830 Observations)

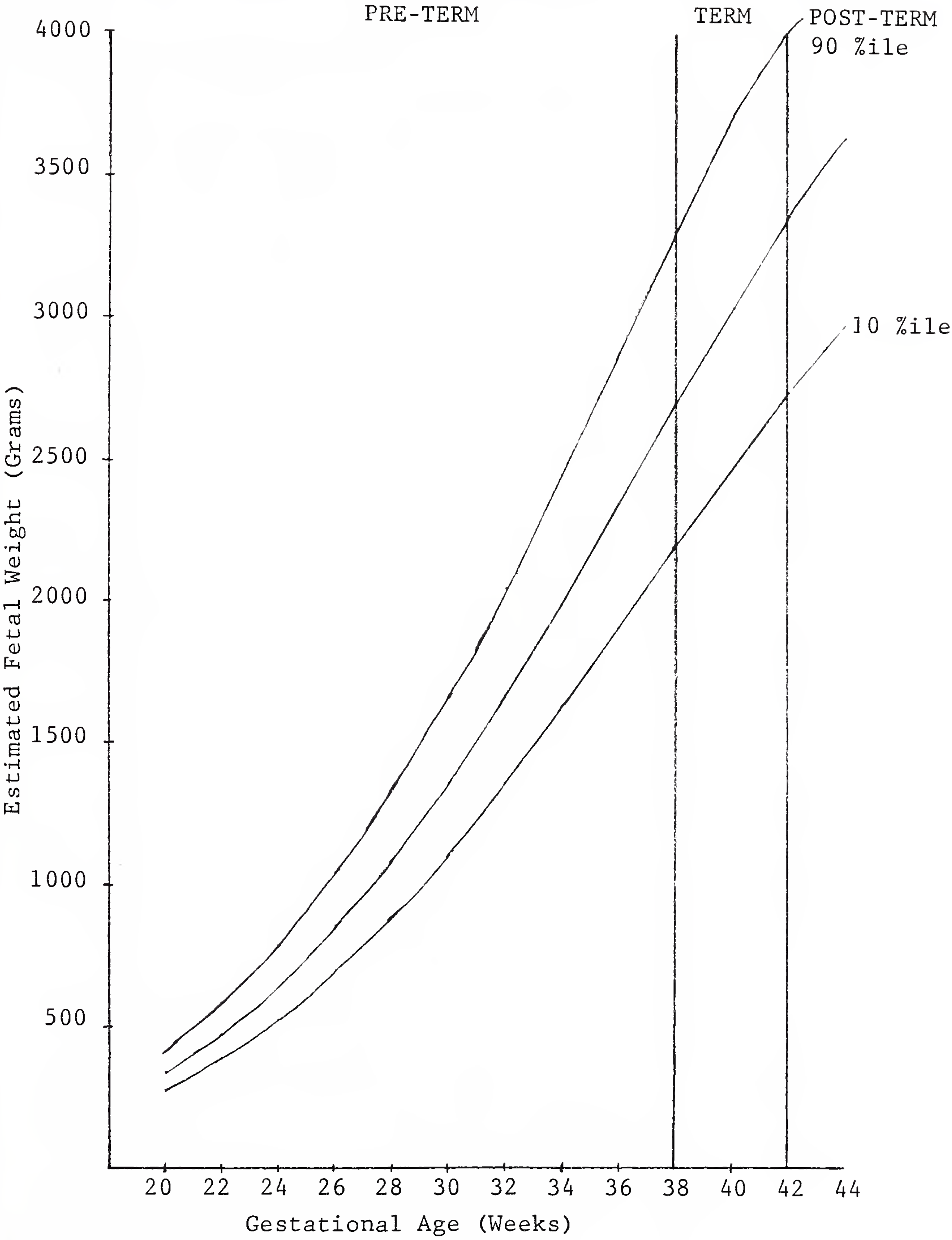
Gestational Age (Weeks)	N	Estimated Fetal Weight (gms) Mean	Std. Dev.
15	1	134.00	-
16	0	0.00	-
17	3	212.67	21.03
18	3	243.67	21.55
19	3	322.33	95.00
20	3	332.33	30.44
21	10	374.60	45.91
22	6	463.17	76.20
23	13	577.85	88.95
24	17	612.06	86.39
25	16	720.12	128.18
26	24	873.83	144.42
27	35	979.54	137.33
28	40	1085.42	177.87
29	39	1323.08	233.64
30	44	1396.77	271.43
31	59	1556.93	246.10
32	62	1672.74	247.19
33	62	1797.05	308.16
34	61	1985.61	324.80
35	75	2220.35	280.19
36	80	2350.79	399.47
37	73	2589.60	483.90
38	43	2600.98	403.50
39	30	2920.30	513.86
40	17	3269.47	455.18
41	7	3082.29	462.79
42	2	3890.00	297.00
43	2	3970.00	307.51

FIGURE 5



Standard Curve of Estimated Fetal Weight
using Summary Statistics
(a)

FIGURE 5



Standard Curve of Estimated Fetal Weight using the Mathematical Model

(b)

MATHEMATICAL MODELS OF EFW

The 830 observations in Groups III and IV were used to derive a mathematical model for estimated fetal weight based on some function of gestational age. An automatic step-wise regression scheme was utilized with the independent variables square root of the gestational age, gestational age, gestational age squared and gestational age cubed. The automatic step-wise inclusion function produced serial multiple regressions including, at each step, the next independent term which explained the greatest portion of the remaining variability, given the existing equation. All designs with estimated fetal weight as a dependent variable; they are, therefore, not reported here and the appropriate logarithmic transformation of estimated fetal weight was done. The results are shown in Table 3. Two independent terms were included, the square root of gestational age and gestational age squared, with a coefficient of determination of 0.91. The standard error of the estimate is +174 or -148 gm/kg. The final model is:

$$\text{Log EFW} = -1.23 + 0.893\sqrt{GA} - 0.000581\ GA^2$$

SUMMARY STATISTICS FOR BIRTH WEIGHT

The birth weights of the infants born to women in Groups III and IV, where known, were summarized in an

TABLE 3

Regressions for the Standard Curve of

Estimated Fetal Weight

Design	R^2	Std. Error (gm/kg)
Attempted:		
Log EFW = f ($\sqrt{GA}$, GA, GA^2, GA^3)		
Log EFW = f ($\sqrt{GA}$)	0.90	+187 -158
Log EFW = f ($\sqrt{GA}$, GA^2)	0.91	+174 -148

Other design variables did not explain sufficient remaining variability to warrant entry.

Final Equation

$$\text{Log EFW} = -1.23 + 0.893\sqrt{GA} - 0.000581\ GA^2$$

All designs with EFW as the dependant variable have divergent plots of Residual vs. Dependent variable; they are, therefore, not reported and the appropriate logerithmic transformation was done (above).

Legend: EFW - Estimated Fetal Weight

GA - Gestational Age

identical manner to estimated fetal weight above. They are shown in Table 4. This group consisted of 398 women. The earliest gestational age at birth was 23 weeks with a birth weight of 810 grams and the latest gestational age at birth was 44 weeks with a birth weight of 3,500 grams. As with estimated fetal weight, it will be noticed that the lower classes and the highest class show a paucity of observations. The same precautionary measure of lumping classes together was taken before using these figures to code the birth weights with regard to the 10th percentile. Also, as for estimated fetal weights, the 10th percentile level was calculated using figures from a Student's t distribution. These data are shown graphically in Figure 5b.

CROSSTABULATION OF EFW AGAINST TIUV

Using the full 830 data points in Groups III and IV, the coded estimated fetal weight was crosstabulated against the coded total intrauterine volume. Although there are estimated fetal weights for all 830 data points there were only 777 readings for total intrauterine volume. Estimated fetal weight was coded into two categories OK and IUGR; total intrauterine volume was coded into three categories OK, gray-zone, and IUGR. The exact definitions of the coding may be found in Table 8. The results of

TABLE 4

Summary Statistics of Birth Weights

by Women in Groups III and IV

(398 Women)

Gestational Age at Birth (Weeks)	N	Birth Weight (gms) Mean	Std. Dev.
23	1	810.00	-
24	3	678.00	32.05
25	2	621.50	75.66
26	2	978.00	220.62
27	3	983.33	241.73
28	7	1123.57	211.40
29	2	1177.50	109.60
30	2	1325.00	205.06
31	4	1365.00	440.47
32	5	1495.00	242.18
33	3	2005.00	256.08
34	8	2293.12	627.10
35	11	2543.18	1192.38
36	20	2640.25	355.93
37	36	2842.50	459.74
38	56	2867.68	458.00
39	80	3131.61	479.14
40	67	3192.84	432.41
41	46	3377.07	497.27
42	24	3514.79	556.70
43	15	3590.33	545.49
44	1	3500.00	-

TABLE 5

Coded Crosstabulation of Estimated Fetal Weight

Against Total Intrauterine Volume

CTIUV

CEFWT	COUNT / ROW PCT / COL PCT / TOT PCT	OK	GRAY ZONE	IUGR	ROW TOTAL
OK	COUNT	573	54	92	719
	ROW PCT	79.7	7.5	12.8	92.5
	COL PCT	95.8	83.1	80.7	
	TOT PCT	73.7	6.9	11.8	
IUGR	COUNT	25	11	22	58
	ROW PCT	43.1	19.0	37.9	7.5
	COL PCT	4.2	16.9	19.3	
	TOT PCT	3.2	1.4	2.8	
	COLUMN TOTAL	598	65	114	777
		77.0	8.4	14.7	100.0

RAW CHI SQUARE = 40.86671 WITH 2 DEGREES OF FREEDOM.

SIGNIFICANCE = 0.0000

(a)

CTIUV

CEFWT	COUNT / ROW PCT / COL PCT / TOT PCT	OK	GRAY ZONE	IUGR	ROW TOTAL
OK	COUNT	566	50	85	701
	ROW PCT	80.7	7.1	12.1	90.2
	COL PCT	94.6	76.9	74.6	
	TOT PCT	72.8	6.4	10.9	
IUGR	COUNT	32	15	29	76
	ROW PCT	42.1	19.7	38.2	9.8
	COL PCT	5.4	23.1	25.4	
	TOT PCT	4.1	1.9	3.7	
	COLUMN TOTAL	598	65	114	777
		77.0	8.4	14.7	100.0

RAW CHI SQUARE = 57.99066 WITH 2 DEGREES OF FREEDOM.

SIGNIFICANCE = 0.0000

(b)

Legend: see Table 8

the crosstabulation may be seen in Table 5. It will be noticed that two runs were done, one using the Table values for coding estimated fetal weights (Table 5a) and the other using the mathematical model for coding estimated fetal weight (Table 5b). It should be noted that the two methods do not differ significantly from one another. Both methods show a significantly large Chi square to indicate interdependence with a probability of error of less than 0.0001.

CROSSTABULATION OF EFW, TIUV AND HEAD-TO-BODY RATIO AGAINST BIRTH WEIGHT

Using the data base of 398 women who gave birth in Groups III and IV, estimated fetal weight coded by both table and by the mathematical model were crosstabulated against the coded birth weight. Total intrauterine volume was also coded and crosstabulated with birth weight. This same coding and crosstabulation was done for the head-to-body ratio. These four crosstabulations will be found in Tables 6a through 6d respectively. The Legend will be found in Table 8. The two methods of coding estimated fetal weight once again do not show significant difference from one another. The crosstabulations of estimated fetal weight against birth weight show small enough Chi square values that the hypothesis of independence cannot

TABLE 6

Coded Crosstabulation of Estimated Fetal Weight, Total Intrauterine Volume, and Head-to-Body Ratio Against Birth Weight

CEFWT by CWT (COUNT / ROW PCT / COL PCT / TOT PCT)

CEFWT		OK	IUGR	ROW TOTAL
OK	COUNT	355	19	374
	ROW PCT	94.9	5.1	94.0
	COL PCT	94.7	82.6	
	TOT PCT	89.2	4.8	
IUGR	COUNT	20	4	24
	ROW PCT	83.3	16.7	6.0
	COL PCT	5.3	17.4	
	TOT PCT	5.0	1.0	
COLUMN TOTAL		375	23	398
		94.2	5.8	100.0

CORRECTED CHI SQUARE = 3.63607 WITH 1 DEGREE OF FREEDOM.
SIGNIFICANCE = 0.0565

(a)

CEFWF by CWT (COUNT / ROW PCT / COL PCT / TOT PCT)

CEFWF		OK	IUGR	ROW TOTAL
OK	COUNT	349	19	368
	ROW PCT	94.8	5.2	92.5
	COL PCT	93.1	82.6	
	TOT PCT	87.7	4.8	
IUGR	COUNT	26	4	30
	ROW PCT	86.7	13.3	7.5
	COL PCT	6.9	17.4	
	TOT PCT	6.5	1.0	
COLUMN TOTAL		375	23	398
		94.2	5.8	100.0

CORRECTED CHI SQUARE = 2.06569 WITH 1 DEGREE OF FREEDOM.
SIGNIFICANCE = 0.1506

(b)

Legend: see Table 8

TABLE 6 (Cont.)

CTIUV	COUNT / ROW PCT / COL PCT / TOT PCT	CWT: OK	CWT: IUGR	ROW TOTAL
OK		284	12	296
		95.9	4.1	80.0
		81.6	54.5	
		76.8	3.2	
GRAY ZONE		9	0	9
		100.0	0.0	2.4
		2.6	0.0	
		2.4	0.0	
IUGR		55	10	65
		84.6	15.4	17.6
		15.8	45.5	
		14.9	2.7	
	COLUMN TOTAL	348	22	370
		94.1	5.9	100.0

RAW CHI SQUARE = 12.81810 WITH 2 DEGREES OF FREEDOM.

SIGNIFICANCE = 0.0016

(c)

CHBR	COUNT / ROW PCT / COL PCT / TOT PCT	CWT: OK	CWT: IUGR	ROW TOTAL
OK		175	15	190
		92.1	7.9	94.5
		95.6	83.3	
		87.1	7.5	
IUGR		8	3	11
		72.7	27.3	5.5
		4.4	16.7	
		4.0	1.5	
	COLUMN TOTAL	183	18	201
		91.0	9.0	100.0

CORRECTED CHI SQUARE = 2.70708 WITH 1 DEGREE OF FREEDOM.

SIGNIFICANCE = 0.0999

(d)

Legend: see Table 8

be rejected. The significance numbers are all greater than 0.05. The crosstabulation of head-to-body ratio with birth weights also shows a small Chi square and a probability of greater than 0.05; therefore, the presumption of independence cannot be rejected. In contrast, the crosstabulation of total intrauterine volume against birth weight (Table 6c) shows a sufficiently larger Chi square that some interdependence can be assumed with a probability of error of less than 0.01.

CROSSTABULATION OF EFW AGAINST TIUV CONTROLLING FOR BIRTH WEIGHT

Using the data base of 398 women who gave birth in Groups III and IV, estimated fetal weight was crosstabulated against total intrauterine volume controlling for birth weight. Estimated fetal weight coded by the table data is shown in Table 7a; estimated fetal weight coded by the mathematical model is shown in Table 7b. The Legends are in Table 8. The results between the two methods for estimated fetal weight are once again not significantly different. When the birth weight fell above the 10th percentile for gestational age (i.e., coded birth weight is OK), the Chi square for estimated fetal weight against total intrauterine volume is sufficiently large to imply an interdependence with a probability of error

TABLE 7

Coded Crosstabulation of Estimated Fetal Weight against Total Intrauterine Volume controlling for Birth Weight

CTIUV

CEFWT (COUNT / ROW PCT / COL PCT / TOT PCT)	OK	GRAY ZONE	IUGR	ROW TOTAL
OK	276 84.1 97.2 79.3	9 2.7 100.0 2.6	43 13.1 78.2 12.4	328 94.3
IUGR	8 40.0 2.8 2.3	0 0.0 0.0 0.0	12 60.0 21.8 3.4	20 5.7
COLUMN TOTAL	284 81.6	9 2.6	55 15.8	348 100.0

RAW CHI SQUARE = 31.27490 WITH 2 DEGREES OF FREEDOM.

SIGNIFICANCE = 0.0000

CWT = OK

CTIUV

CEFWT (COUNT / ROW PCT / COL PCT / TOT PCT)	OK	IUGR	ROW TOTAL
OK	11 57.9 91.7 50.0	8 42.1 80.0 36.4	19 86.4
IUGR	1 33.3 8.3 4.5	2 66.7 20.0 9.1	3 13.6
COLUMN TOTAL	12 54.5	10 45.5	22 100.0

CORRECTED CHI SQUARE = 0.02895 WITH 1 DEGREE OF FREEDOM.

SIGNIFICANCE = 0.8649

CWT = IUGR

(a)

Legend: see Table 8

TABLE 7 (Cont.)

CEFWT by CTIUV (COUNT / ROW PCT / COL PCT / TOT PCT)

CEFWT		OK	GRAY ZONE	IUGR	ROW TOTAL
OK	COUNT	275	8	41	324
	ROW PCT	84.9	2.5	12.7	93.1
	COL PCT	96.8	88.9	74.5	
	TOT PCT	79.0	2.3	11.8	
IUGR	COUNT	9	1	14	24
	ROW PCT	37.5	4.2	58.3	6.9
	COL PCT	3.2	11.1	25.5	
	TOT PCT	2.6	0.3	4.0	
COLUMN TOTAL		284	9	55	348
		81.6	2.6	15.8	100.0

RAW CHI SQUARE = 35.89490 WITH 2 DEGREES OF FREEDOM.

SIGNIFICANCE = 0.0000

CWT = OK

CEFWF by CTIUV (COUNT / ROW PCT / COL PCT / TOT PCT)

CEFWF		OK	IUGR	ROW TOTAL
OK	COUNT	11	8	19
	ROW PCT	57.9	42.1	86.4
	COL PCT	91.7	80.0	
	TOT PCT	50.0	36.4	
IUGR	COUNT	1	2	3
	ROW PCT	33.3	66.7	13.6
	COL PCT	8.3	20.0	
	TOT PCT	4.5	9.1	
COLUMN TOTAL		12	10	22
		54.5	45.5	100.0

CORRECTED CHI SQUARE = 0.02895 WITH 1 DEGREE OF FREEDOM.

SIGNIFICANCE = 0.8649

CWT = IUGR

(b)

Legend: see Table 8

TABLE 8

Legend Coding for Tables 5, 6 and 7

CEFWT = Estimated Fetal Weight Coded by Table data

OK $\geq$ 10th %ile

IUGR $<$ 10th %ile

CEFWF = Estimated Fetal Weight Coded by Formula data

OK $\geq$ 10th %ile

IUGR $<$ 10th %ile

CTIUV = Total Intrauterine Volume Coded by Original results (35)

OK $\geq$ -1.0 std. dev.

GRAY ZONE $<$ -1.0 std. dev. and $\geq$ -1.5 std. dev.

IUGR $<$ -1.5 std. dev.

CHBR = Head-to-Body Ratio Coded by authors data (17)

OK $\leq$ 95th %ile

IUGR $>$ 95th %ile

CWT = Birth Weight Coded by Table data

OK $\geq$ 10th %ile

IUGR $<$ 10th %ile

less than 0.0001. However, when the birth weight fell in the range less than the 10th percentile (i.e., coded birth weight is IUGR), the presumption of independence between estimated fetal weight and total intrauterine volume cannot be rejected; the Chi squares were quite low and the probability of error ran about 86%.

MATHEMATICAL MODELS FOR BIRTH WEIGHT PREDICTIONS

Using the data base of the 398 women who gave birth in Groups III and IV, mathematical models were attempted to predict the eventual birth weight from the current parameters at a particular examination date and a projected birth date. The gestational age of the exam, the estimated fetal weight, the total intrauterine volume, the head-to-body ratio and the Z-square for estimated fetal weight (i.e., the number of standard deviations above or below the mean that particular measurement is within its own gestational age class). Once again, all the designs using the untransformed weight as the dependent variable had divergent plots of residual versus the dependent variable. They have not been reported, and the appropriate logarithmic transformation was done.

The first model attempt used the gestational age at birth, the gestational age at the exam, the estimated fetal weight, the total intrauterine volume, the head-to-body ratio, all their squared terms, and the cross-products

of gestational age with total intrauterine volume, estimated fetal weight, and head-to-body ratio. This all inclusive model used only 198 of the 398 cases since a case was dropped when any variable was missing. It was attempted in order to find the general direction for subsequent models. The results are shown in Table 9a. The best result came at a coefficient of determination of 0.82, a standard error of the estimate of +144 or -126 gm/kg and included six independent variables. The formula is as follows:

$$\text{Log BW} = 0.151 + 0.153\ \text{GAB} - 0.00167\ \text{GAB}^2 - 0.150\ \text{TIUV}^2/10^4 - 0.000431\ \text{GA}^3 + 0.512\ \text{GA.TIUV}/10^5$$

The second attempt used the gestational age at birth, the estimated fetal weight to gestational age ratio, the total intrauterine volume to gestational age ratio, and all their squared terms. These ratios were added because it was felt that the estimated fetal weight or total intrauterine volume at a particular gestational age might explain an ultimate birth weight. The best equation had four terms, a coefficient of determination of 0.79 and a standard of the estimate of +156 or -135 gm/kg. The final equation is:

$$\text{Log BW} = 0.926 + 0.146\ \text{GAB} + 0.00188\ \text{TIUV/GA} - 0.00158\ \text{GAB}^2 - 0.00113\ \text{EFW/GA}$$

The results are shown in Table 9b.

TABLE 9

REGRESSIONS FOR PREDICTING BIRTH WEIGHT

All designs with EFW as the dependent variable have divergent plots of Residual vs. Dependent Variable; they are, therefore, not reported and the appropriate logarithmic transformation was done.

The Legend for all of Table 9 is:

BW = Birth weight

GAB = Gestational age at birth

EFW = Estimated fetal weight

TIUV = Total intrauterine volume

HBR = Head-to-body ratio

GA = Gestational age at examination

ZT = EFW Z-score calculated from summary statistics

ZF = EFW Z-score calculated from the derived formula

TABLE 9 (Cont.)

Design	R^2	Std.Error gm/kg
Attempted:		
Log BW = f (GAB, GAB2, GA, GA^2, EFW, EFW^2, TIUV, $TIUV^2$, HBR, HBR^2, GA.TIUV, GA.EFW. GA.HBR)		
Log BW = f (GAB)	0.62	+209 -173
= f (GAB, GAB^2)	0.70	+184 -156
= f (GAB, GAB^2, $TIUV^2$)	0.74	+173 -147
= f (GAB, GAB^2, $TIUV^2$, GA^2)	0.80	+150 -131
= f (GAB, GAB^2, $TIUV^2$, GA^2, GA.TIUV)	0.82	+144 -126

Other design variables did not explain sufficient remaining variability to warrant entry.

Final Equation:

$$\text{Log BW} = 0.151 + 0.153\text{GAB} - 0.00167\ \text{GAB}^2 - 0.150\ \text{TIUV}^2/10^7 - 0.000431\ \text{GA}^3 + 0.512\ \text{GA.TIUV}/10^5$$

(a)

TABLE 9 (Cont.)

Design	R^2	Std. Error (gm/kg)
Attempted:		
Log BW = f (GAB, GAB^2, EFW/GA, EFW^2/GA, TIUV/GA, $TIUV^2$/GA)		
Log BW = f (GAB)	0.67	+198 -165
= f (GAB, TIUV/GA)	0.73	+179 -152
= f (GAB, TIUV/GA, GAB^2)	0.78	+161 -138
= f (GAB, TIUV/GA, GAB^2, EFW/GA)	0.79	+156 -135

Other design variables did not explain sufficient remaining veriability to warrant entry.

Final Equation:

$$\text{Log BW} = 0.926 + 0.146\ \text{GAB} + 0.00188\ \text{TIUV/GA} - 0.00158\text{GAB}^2 - 0.00113\ \text{EFW/GA}$$

(b)

TABLE 9 (Cont.)

Design	R^2	Std. Error (gm/kg)
Attempted:		
Log BW = f (GAB, GAB^2, EFW/GA, EFW^2/GA)		
Log BW = f (GAB)	0.73	+196 -164
= f (GAB, GAB^2)	0.77	+180 -152
= f (GAB, GAB^2, EFW^2/GA)	0.78	+176 -150

Other design variable did not explain sufficient remaining variability to warrant entry.

Final Equation:

$$\text{Log BW} = 0.371 + 0.136\text{GAB} - 0.00146\text{GAB}^2 + 0.164\text{EFW}^2/\text{GA}/10^6$$

(c)

TABLE 9 (Cont.)

Design	R^2	Std. Error (gm/kg)
Attempted:		
Log BW = f ($\sqrt{GAB}$, GAB, GAB^2, GAB^3, (Log EFW)/GA, (log EFW)/$\sqrt{GA}$)		
Log BW = f ($\sqrt{GAB}$)	0.75	+191 -160
= f ($\sqrt{GAB}$, (Log EFW)/$\sqrt{GA}$)	0.79	+173 -148
= f ($\sqrt{GAB}$, (Log EFW)/$\sqrt{GA}$, GAB^3)	0.81	+165 -141

Other design variables did not explain sufficient remaining variability to warrant entry.

Final Equation:

$$\text{Log BW} = -2.13 + 0.782\sqrt{GAB} + 2.12\,(\text{Log EFW})/\sqrt{GA} - 0.793\,GAB^3/10^5$$

(d)

TABLE 9 (Cont.)

Design	R^2	Std. Error (gm/kg)
Attempted:		
Log BW = f ($\sqrt{GAB}$, GAB, GAB^2, GAB^3, ZT)		
Log BW = f ($\sqrt{GAB}$)	0.75	+191 -160
= f ($\sqrt{GAB}$, ZT)	0.80	+170 -145
= f ($\sqrt{GAB}$, ZT, GAB^3)	0.82	+159 -137

Other design variables did not explain sufficient remaining variability to warrant entry.

Final Equation:

$$\text{Log BW} = -0.969 + 0.794\sqrt{GAB} + 0.0350\ ZT - 0.855\ GAB^3/10^5$$

(e)

TABLE 9 (Cont.)

Design	R^2	Std. Error (gm/kg)
Attempted:		
Los BW = f ($\sqrt{GAB}$, GAB, GAB^2, GAB^3, ZF)		
Log BW = f ($\sqrt{GAB}$)	0.75	+191 -160
= f ($\sqrt{GAB}$, ZF)	0.79	+174 -148
= f ($\sqrt{GAB}$, ZF, GAB^3)	0.81	+165 -142

Other design variables did not explain sufficient remaining variability to warrant entry.

Final Equation:

$$\text{Log BW} = -0.835 + 0.766\sqrt{GAB} + 0.0300\ ZF - 0.789\ GAB^3/10^5$$

(f)

The next attempt was similar to the former, just dropping the total intrauterine volume to gestational age ratios in order to allow for more cases to enter into the determination of the model. The best equation contained three terms, a coefficient of determination of 0.78, and a standard error of the estimate of +176 or -150 gm/kg. The equation is:

$$\text{Log BW} = 0.371 + 0.136\text{GAB} - 0.00146\text{GAB}^2 + 0.164\text{EFW}^2/\text{GA}/10^6$$

The results are shown in Table 9c.

In the modeling of estimated fetal weight (see above), using the various powers of the gestational age proved advantageous. Therefore, in the next attempt all the powers of the gestational age at birth from square root to third power plus the ratio of the log of the estimated fetal weight to the gestational age at the examination, log of the estimated fetal weight to the square root of the gestational age at the examination were used as the dependent variables. The best fit was arrived at with three terms, a coefficient of determination of 0.81, and a standard error of the estimate of +165 or -141 gm/kg. The final equation is:

$$\text{Log BW} = 2.13 + 0.782\sqrt{\text{GAB}} + 2.12\ (\text{Log EFW})/\sqrt{\text{GA}}$$

The results will be found in Table 9d.

The next two attempts again use the same series of powers of the gestational age at birth, and the Z-score

of the estimated fetal weight; the two methods differ only in the calculation of the Z-score either by the table data or by the mathematical model. The rationale behind this is that although the final birth age is the primary determinant, where the infant placed earlier, in terms of a standardized figure such as a Z-score, could be a good predictor. Both these attempts gave similar results. The one using the table value of the Z-score has three terms, a coefficient of determination of 0.82, and a standard error of the estimate of +159 or -137 gm/kg. The equation is:

$$\text{Log BW} = -0.969 + 0.794 \text{ GAB} + 0.0350 \text{ ZT} - 0.855 \text{ GAB}^3/10^5$$

The results may be found in Table 9d. The equation using the Z-score derived using the mathematical model also has three terms, a coefficient of determination of 0.81, and standard error of the estimate of +165 or -142 gm/kg. The equation is:

$$\text{Log BW} = -0.835 + 0.766 \text{ GAB} + 0.0300 \text{ ZF} - 0.789 \text{ GAB}^3/10^5$$

The results may be found in Table 9f.

Of the six attempts, four had coefficients of determination showing explanation of approximately 81-82% of the variability of the dependent variable. These four are those listed in Tables 9a, 9d, 9e and 9f. Their standard errors of the estimate are also comparable. The other two models have coefficients of determination

only slightly less (78-79%) and standard errors of the estimate only slightly higher.

REGRESSION OF ESTIMATED FETAL WEIGHT VERSUS BIRTH WEIGHT

The entire 1281 data points were searched to find those where the birth was affected within 48 hours of the estimated fetal weight determination, in order to reverify the validity of the estimated fetal weight formula. A sub-set of 80 women fulfilled this condition. The formula is:

$$BW = 308.18 + 0.946 \ EFW$$

The coefficient of determination is 0.90, the standard error of the estimate is 310.17, and the standard error of the coefficient is 0.0355. Dividing the constant term by the standard error of the estimate to obtain a t-value for the intercept, yields a very small number, indicating that the intercept does not significantly differ from 0. If the slope of 0.946 is subtracted from one and then divided by the standard error of the coefficient, a t-value of 1.53 is obtained. This shows that the slope does not significantly differ from 1.0. The standard error of the estimate may be thought of as an average, since we are aware that the error is less at small weights and more at larger weights.

SECTION 10

DISCUSSION

THE STANDARD CURVE OF ESTIMATED FETAL WEIGHT

The currently accepted nomogram for birth weight against week of gestation was designed by Lubchenco, et al, (52) using the data for infants born at the University of Colorado Medical Center between 1958 and 1969. The study group comprised over 1600 infants spread across the pre-term, term, and post-term periods of gestation. The use of this nomogram as a gauge for estimated fetal weights by ultrasound has been a necessity due to the lack of any other suitable standard. It is, however, subject to the following biases. The data on which Lubchenco's study is based is made up of infants born in Denver, Colorado which is approximately 1 mile above sea level. The population mix may also be radically different from that found in typical east coast cities. In addition, although the estimated fetal weight approximates the actual weight of the fetus, it would seem prudent to evaluate estimated fetal weights against a standard curve of estimated fetal weights and not against a standard curve of actual birth weights. This is because estimated fetal weight may differ in some amount from the true weight of the fetus. In addition, the estimated fetal weight

standard curve is based on fetuses that are still in utero, whereas the birth weights curve is based on infants that are already ex utero. At the lower end of the scale, there is no reason to assume that the weight distribution of infants who remained in utero is the same as those that are prematurely born. This latter group may belong to a totally different population.

The standard curve is represented in two fashions in Figures 5a and 5b. Figure 5a is based on the direct plotting of the summary statistics and Figure 5b is the plot of the calculated mathematical model. As will be noted from the results in other sections of the experiment, the results derived using either did not differ significantly from one another. Therefore, one may use either as the standard curve, providing that one is consistent. These curves will be most accurate between approximately the 23rd and 40th weeks, and least accurate above and below these dates. This is due to the paucity of observations of the extremes of gestational age. The fact that caution should be used in interpreting any standard derived from these areas should be obvious.

As with any new set of standards based on retrospective data, these nomograms should be checked out on a prospective basis.

ESTIMATED FETAL WEIGHT AS A TEST FOR IUGR

It is extremely difficult to evaluate whether a given measure is an accurate test for IUGR while the fetus is still in utero. The eventual outcome, IUGR at birth, may be many weeks in the future. In addition, the outcome may be affected by a therapy which was prescribed. Over the past two years, it has been routine procedure in this perinatal unit to prescribe bed rest in the left lateral decubitus position when IUGR is suspected. It has been found that with this therapy, parameters evaluating IUGR such as the total intrauterine volume and the estimated fetal weight, frequently make substantial gains. It is assumed that this is due to the improved blood flow to the placenta effected by removing the pressure of the uterus on the major blood vessels. This would naturally bias the eventual outcome and make it suspect in judging an earlier indicator. A suitable test would be to use those data points where birth was affected within 48 hours of an estimated fetal weight measurement and where the gestational age was known with reasonable certainty (i.e., Groups III and IV). The former sub-set consisted of only 80 data points which means that both conditions will be fulfilled by approximately 40 cases. This is obviously too little to be statistically meaningful.

Gohari, et al (35), has shown that the total intrauterine volume is reliable as a screening test for IUGR. Although this will not give us 100% certainty as to whether the infant is IUGR or not, TIUV will be used as the control for the estimated fetal weight. Table 5 shows the coded crosstabulation of estimated fetal weight against total intrauterine volume. The Chi square is large enough to indicate an interdependence between estimated fetal weight and total intrauterine volume with a chance of error of less than 0.0001. If it is assumed that IUGR by coded total intrauterine volume is in fact correct, then the false negative rate for estimated fetal weight, which runs between 75 and 80%, is in fact unacceptable. It will be noted, however, that if we consider those coded OK by total intrauterine volume as in fact indicating no IUGR, then the false positive rate is only between 4 and 5%. This will allow us the leeway in future studies to raise the IUGR cut-off for estimated fetal weight higher than the 10th percentile. This would lower the false negative rate at the expense of the false positive rate. We are obviously more concerned with catching all cases of IUGR than the chance of presuming IUGR where it does not exist. This is not to say that the latter case is not without significant problems, as it is bound to cause a woman undue worry and have her activity restricted unnecessarily.

There is another alternative explanation of these data. If it is assumed that both the total intrauterine volume and the estimated fetal weight are imperfect indicators of IUGR, then both may be assessing IUGR in different instances, each with its own false positive and false negative rates. In that instance, it would be unfair to use one of these measures as a control for the other. The only answer to this dilemma, would be to do a prospective study over many years, where individual cases were selected, with birth of the fetus affected within a reasonable time after both the total intrauterine volume and the estimated fetal weight had been calculated.

PREDICTION OF IUGR AT BIRTH

As indicated above the eventual outcome of the pregnancy may be many weeks removed from the initial or subsequent examinations and, therefore, may not be a true indicator of its validity. However, Table 6 shows the coded crosstabulations of three evaluators of IUGR (estimated fetal weight, total intrauterine volume, and head-to-body ratio) against the final birth weight. It will be noted that the Chi square for estimated fetal weight and head-to-body ratio against birth weight are relatively small and do not indicate any deviation from independence. On the other hand, the total intrauterine volume, Table 6c, does show a significant Chi square

indicating an interdependence between total intrauterine volume and the eventual birth weight with a probability of error of less than 0.01. It will be noted, however, that the false negative rate is 55% and the false positive rate about 16%, numbers which are far at variance from those shown in the studies (21, 35). This finding once again places in question the validity of using an eventual birth weight as a control for a parameter derived much earlier. Conversely, it may be said, that these three parameters are not measures of IUGR at birth, or birth is affected at a time substantially different from the time of the measurement. What they may in fact indicate, but which has not been proved here, is IUGR at the time of examination. The same prospective study would have to be done as indicated in the previous section.

PROJECTION OF BIRTH WEIGHT

In light of the previous finding that the parameters estimated fetal weight, total intrauterine volume and head-to-body ratio measured earlier in the pregnancy do not predict IUGR at birth, it might seem incongruous to attempt to use these same parameters to predict eventual birth weight. In fact, this may be a reasonable thing to do. One of the reasons that IUGR at birth may not be predicted by an earlier measured parameter may be the intervening therapy. If it is assumed that this therapy

is automatically instituted to all women suspected of carrying an IUGR fetus, then the earlier parameters merely set a point on the curve which may be then followed to eventual delivery, the affects of the therapy included.

All these six models attempted yielded remarkably similar coefficients of determination and standard errors of the estimate. The best two models, both with coefficients of determination of 0.82 are shown in Table 9a and Table 9e. The former relates log birth weight to the projected gestational age at birth, the total intrauterine volume and the gestational age at the examination. The latter relates log of the birth rate to the gestational age at birth and the Z-score of the estimated fetal weight. The formulas are:

$$\text{Log BW} = 0.151 + 0.153\ \text{GAB} - 0.00167\ \text{GAB}^2 - 0.150\ \text{TIUV}^2/10^7 - 0.000431\ \text{GA}^3 + 0.512\ \text{GA.TIUV}/10^5 \quad (1)$$

$$\text{Log BW} = -\ 0.969 + 0.794\ \text{GAB} + 0.350\ \text{ZT} - 0.855\ \text{GAB}^3/10^5 \quad (2)$$

Formula 1 has the advantages of having a slightly better standard error of the estimate and the ability to use parameters which are fairly easy to determine (the total intrauterine volume being easier to measure than the estimated fetal weight). Formula 2 has the advantage of being a simple formula with three terms versus six: a two way table can be constructed giving projected gestational age at birth in one direction and Z-score at the examination along the other.

Let us spend a moment to evaluate the magnitudes of the standard errors of the estimate. It will be noted that two numbers are given for each standard error: a positive and a negative number. This is due to the fact that since there is a logarithmic transformation of the dependent variable the true standard error developed by the regression is added or subtracted from the log of the birth weight. This is equivalent to multiplying or dividing the birth weight by the anti-log of the standard error. To overcome this, two figures are used one for the positive (that is multiplication direction) and one for the negative (division direction). It also means that the standard error is not constant along the curve but changes depending on the magnitude of the dependent variable (i.e., birth weight). Using formula 1 as an example, if a birth weight of 4,000 grams was projected by the formula, the predicted error would be +576 grams or -504 grams. This would seem an unreasonably large error to deal with. However, if we look at a baby with a projected birth weight of 2,000 grams the projected error is +288 or -252 grams, which is more reasonable. The predicted birth weight is, therefore, more accurate precisely in the area where it is needed most, in the evaluation of the smaller, possibly IUGR, fetus. It must be remembered that the original formula for the

calculation of estimated fetal weight had a standard error of the estimate of 106 gm/kg, a number which is not very much better than those shown here and, in addition, this standard error was calculated comparing fetal parameters to birth weights affected within 48 hours.

REVERIFICATION OF THE WARSOF FORMULA

In order to reverify the formula developed by Warsof, et al (75), the assumption was made that a model could be fitted between the estimated fetal weight and the birth weight, where birth is affected within 48 hours, of the following tenor:

$$BW = A + B\ BFW \qquad (3)$$

The coefficient of determination calculated was 0.90 indicating that estimated fetal weight is a very good predictor of weight at birth under these conditions. In addition, if one is to make the assumption that estimated fetal weight is in fact exactly the birth weight then the following must be true: the intercept term (A) must be 0 and the slope term (B) must be equal to 1. The value of the intercept is 309, but when this is divided by the standard error of the estimate of 310 it is obvious that there is no significant deviation from 0. The coefficient B is 0.946, a difference of 0.054 from 1. If this is divided by the standard error of B (0.036) a t-value of 1.5 is calculated. This is not large enough at 78 degrees

of freedom to reject the hypothesis that B equals 1. It may, therefore, be concluded that the estimated fetal weight does not significantly differ from the birth weight when birth is affected within 48 hours. The logical explanation of this is that estimated fetal weight is a predictor of the fetal weight at all times during the gestation.

SECTION 11

CONCLUSIONS

1. A standard curve of estimated fetal weight against week of gestation has been constructed. A mathematical model was derived to fit this curve; it has a coefficient of determination of 0.91 and a standard error of the estimate of +174 or -148 gm/kg. Various parameters derived using the raw statistics or the final model did not significantly differ from one another. This model needs further verification using a prospective study. It is most accurate between 23 and 40 weeks of gestation.
2. It was difficult to evaluate whether estimated fetal weight is a good indicator of IUGR due to the inability to ascertain IUGR with 100% accuracy in utero. There was, however, an interdependence between estimated fetal weight and total intrauterine volume. An argument can be made for the assumption that these two parameters are both imperfect indicators of IUGR.
3. None of the current tests was a good predictor of IUGR at birth. This may be due to the temporal separation of examination and birth, and the intervening therapy.
4. Six models were proposed for the prediction of birth weight. The best of these have coefficients of

determination of 0.82 and standard errors of the estimate of approximately +150 or -130 gm/kg. This makes them reasonably accurate at the lower birth weights, where they would be most useful.

5. The Warsof formula for estimated fetal weight was reverified using the data collected in this study.

REFERENCES

1. Arias, F.: The diagnosis and management of intrauterine growth retardation. Obstet Gynecol 49:293, 1977.

2. Aubry, R. H., Beydoun, S., Cabalum, M. T., Williams, M. L.: Fetal growth retardation. Perinatal Medicine Management of the High Risk Fetus and Neonate. Bolognese, R. J., Schwartz, R. H., Editors, (Baltimore: Williams and Wilkins, 1977).

3. Ballantyne, J. W. J.: The problem of the postmature infant. J Obstet Gynaecol Brit Empire 2:521, 1902.

4. Bard, H.: Intrauterine growth retardation. Clin Obstet Gynecol 13:511, 1970.

5. Bard, H.: Neonatal problems of infants with intrauterine growth retardation. J Reprod Med 21:359, 1978.

6. Bartolucci, L.: BPD of the skull and fetal weight in the second trimester: an allometric relationship. Am J Obstet Gynecol 122:439, 1975.

7. Battaglia, F. C., Lubchenco, L. O.: A practical classification of newborn infants by weight and gestational age. J Pediatr 71:159, 1967.

8. Beazley, J. M., Underhill, R. A.: Fallacy of the fundal height. Brit Med J 4:404, 1970.

9. Beischer, N. A., Brown, J. B.: Current status of estrogen assays in obstetrics and gynecology. Obstet Gynecol Surv 27:303, 1972.

10. Belizan, J. M., Villar, J., Nardin, J. C., Malamud, J., DeVicuna, L. S.: Diagnosis of intrauterine growth retardation by a simple clinical method: measurement of uterine height. Am J Obstet Gynecol 131:643, 1978.

11. Bergsjo, D., Bakke, T., Salamonsen, L. A., STØA, K. F., Thorson, T.: Urinary oestriol in pregnancy, daily fluctuation and correlation with fetal growth. J Obstet Gynaecol Br Commonw 80:305, 1973.

12. Berkowitz, R. L., Hobbins, J. C.: Ultrasonography in the antepartum patient. Perinatal Medicine Management of the High Risk Fetus and Neonate. Bolognese, R. J., Schwartz, R., Editors (Baltimore: Williams and Wilkins, 1977).

13. Butler, N. R., Alberman, E. D., Editors: Perinatal Problems: The Second Report of the 1958 British Perinatal Mortality Survey. (Edinburgh: Churchill Livingston Ltd., 1969).

14. Campbell, S.: Fetal growth. Clin Obstet Gynecol 1:41, 1974.

15. Campbell, S.: Fetal Growth. Fetal Physiology and Medicine. Beard, R. W., Nathanielsz, P. W., Editors. (London: W. B. Saunders, 1976).

16. Campbell, S.: Physical methods of assessing size at birth. CIBA Foundation Symposium 27:275, 1974.

17. Campbell, S.: Ultrasound measurement of the fetal head to abdomen circumference ratio in assessment of growth retardation. Br J Gynaecol 84:165, 1977.

18. Campbell, S., Kurjak, A.: Comparison between urinary oestrogen assay and serial ultrasonic cephalometry in assessment of fetal growth retardation. Br Med J 4:336, 1972.

19. Cetrulo, C. L., Freeman, R.: Bioelectric evaluation in intrauterine growth retardation. Clinical Obstetrics and Gynecology. Frigoletto, F. D. Jr., Guest Editor. (Hagerstown, MD: Harper & Row, 1977).

20. Christie, G. B., Cudmore, D. W.: The oxytocin challenge test. Am J Obstet Gynecol 118:327, 1974.

21. DeVore, G. R., Hobbins, J. C.: Fetal growth and development: the diagnosis of intrauterine growth retardation. Clinics in Diagnostic Ultrasound in Obstetrics, Vol. 3. Hobbins, J. C., Editor (New York: Churchill, Livingston, 1979).

22. Dewhurst, C. J., Beazley, J. M., Campbell, S.: Assessment of Fetal maturity and dysmaturity. Am J Obstet Gynecol 113:141, 1972.

23. Donald, I.: Diagnosis of abdominal swellings. Br Med J 2:1154, 1963.

24. Donald, I., Brown, T. G.: Localization using physical devices, radioisotopes and radiographic methods. Br J Radiology 34:405, 1961.

25. Donald, I., MacVicar, J., Brown, T. G.: Investigation of abdominal masses by pulsed ultrasound Lancet 1:1188, 1958.

26. Easterling, W. E., Talbert, L. M.: Estriol excretion in normal and complicated pregnancies. Am J Obstet Gynecol 107:417, 1970.

27. Elliot, P. M.: Urinary Oestriol excretion in retarded intrauterine fetal growth. Aust NZJ Obstet Gynaecol 10:18, 1970.

28. Ewing, D. E., Farina, J. R., Otterson, W. N.: Clinical application of the oxytocin challenge test. Obstet Gynecol 43:563, 1974.

29. Fitzhardinge, P. M., Steven, E. M.: The small for date infant I. Later growth patterns. Pediatrics 49:671, 1972.

30. Fitzhardinge, P. M., Stevens, E. M.: The small for date infant II. Neurological and intellectual sequalae. Pediatrics 50:50, 1972.

31. Frigoletto, F. D., Jr., Rothchild, S. B.: Altered fetal growth: an overview. Clinical Obstetrics and Gynecology. Frigoletto, F. D., Jr., Guest Editor (Hagerstown, MD: Harper & Row, 1977).

32. Galbraith, R. S., Karchmar, E. J., Pievey, W. N., Low, J. A.: The clinical prediction of intrauterine growth retardation. Am J Obstet Gynecol 133:281, 1979.

33. Galbraith, R. S., Low, J. A., Boston, R. W.: Maternal urinary estriol excretion pattern in patients with chronic fetal insufficiency. Am J Obstet Gynecol 106:352, 1970.

34. Gohari, P., Berkowitz, R. L., Hobbins, J. C.: Early diagnosis key to reduction of grave IUGR risks. Contemp Ob/Gyn 8:79, 1976.

35. Gohari, P., Berkowitz, R. L., Hobbins, J. C.: Prediction of intrauterine growth retardation by determination of total intrauterine volume. Am J Obstet Gynecol 127:255, 1977.

36. Goldberg, B. B., Kotler, M. N., Erskin, Waxham. Diagnostic Uses of Ultrasound. (New York: Gruneel Stratton, 1975).

37. Hansman, M. Ultraschallbiometric in II und III trimester der schwangerschaft. Gyna Kologe 9:133, 1976.

38. Hellman, L. M., Kobayashi, M., Fillisti, L., Lavenhar, M.: Sources of error sonographic fetal mesuration and estimation of growth. Am J Obstet Gynecol 99: 669, 1967.

39. Hill, D. E.: Physical growth and development after intrauterine growth retardation. J Reprod Med 21: 355, 1978.

40. Hobbins, J. C., Berkowitz, R. L. Grannum, P. A. T.: Diagnosis and antepartum management of intrauterine growth retardation. J Reprod Med 21:319, 1978.

41. Hobbins, J. C., Winsberg, F.: Ultrasound in Obstetrics and Gynecology. (Baltimore: The Williams & Wilkins Co., 1976).

42. Ianniruberto, A., Gibbons, J. M.: Predicting fetal weight by ultrasound B scan cephalometry. An improved technic with disappointing results. Obstet Gynecol 32:76, 1936.

43. Jones, K. L., Chernoff, G. F.: Drugs and chemicals associated with intrauterine growth deficiency. J Reprod Med 21:365, 1978.

44. Jones, O. W.: Genetic factors in the determination of fetal size. J Reprod Med 21:305, 1978.

45. Josimovich, J. B., Kosor, B., Bocella, L., Mintz, D. H., Hutchinson, D. L.: Placental lactogen in maternal serum as an index of fetal health. Obstet Gynecol 36:244, 1970.

46. Klopper, A.: The assessment of fetoplacental function by estriol assay. Obstet Gynecol Surv 23:813, 1968.

47. Know, G. E.: Influence of infection on fetal growth and development. J Reprod Med 21:352, 1978.

48. Kohorn, E. L.: An evaluation of ultrasonic fetal cephalometry. Am J Obstet Gynecol 97:553, 1967.

49. Kruger, H., Arias-Stella, J.: The placenta and the newborn infant at high altitudes. Am J Obstet Gynecol 106:586, 1970.

50. Loeffler, F. E.: Clinical fetal weight prediction. Br J Obstet Gynaecol 74:675, 1967.

51. Low, J. A., Galbraith, R. S.: Pregnancy characteristics of intrauterine growth retardation. Obstet Gynecol 44:122, 1970.

52. Lubchenco, L. O., Hansman, C., Boyd E.: Intrauterine growth in length and head circumference as estimated from live births at gestational age from 26-42 weeks. Pediatrics 37:403, 1966.

53. Lunt, R. M., Chard, T.: A new method for estimation of fetal weight in late pregnancy by ultrasonic scanning. Br J Obstet Gynaecol 83:1, 1976.

54. Lunt, R. M., Chard, T.: Reproducibility of measurement of fetal BPD by ultrasound cephalometry. J Obstet Gynaecol Br Comm 81:366, 1974.

55. Mac Mahon, B., Alpert, M., Salber, E. J.: Infant weight and parental smoking habits. Am J Epidemiology 82:247, 1966.

56. Mann, L. I., Tejani, N. A., Weiss, R. R.: Antenatal diagnosis and management of the small-for-gestational-age fetus. Am J Obstet Gynecol 120:995, 1974.

REFERENCES (Cont.)

57. Martin, J. D., Hahnel, R., Kean, B. P., Troy, V. G.: Urinary oestrogen excretion in women with intrauterine fetal growth retardation. Aust NZ J Obstet Gynaecol 12:102, 1972.

58. Michie, E. A.: Urinary Oestriol excretion in pregnancies complicated by suspected retarded intrauterine growth, toxaemia, or essential hypertension. J Obstet Gynaecol Br Commonw 74:896, 1967.

59. Parer, J. T., Afonso, J. F.: Validity of the weekly interval between oxytocin challenge tests. Am J Obstet Gynecol 127:204, 1977.

60. Resnik, R.: Maternal diseases associated with abnormal fetal growth. J Reprod Med 21:315, 1978.

61. Russel, J. G. B., Jones. The uses and possible hazards of diagnostic ultrasound in medicine. Physiotherapy 59:279, 1973.

62. Sabbagha, R. E.: Intrauterine growth retardation antenatal diagnosis by ultrasound. Obstet Gynecol 52:252, 1978.

63. Sabbagha, R. E., Hughey, M., Depp, R.: Growth adjusted sonographic age: a simplified method. Obstet Gynecol 51:383, 1978.

64. Schifrin, B. S., Et Al: Contraction stress test for antepartum fetal evaluation. Obstet Gynecol 45:433, 1975.

65. Spellacy, W. N.: Monitoring of high-risk pregnancies with human placental lactogen. Management of the High Risk Pregnency. Spellacy, W. N., Editor. (Baltimore, University Park Press, 1976).

66. Thompson, H. E., Holmes, J. H., Gottesfeld, K. R., Taylor, E. S.: Fetal development as determined by ultrasonic pulse echo techniques. Am J Obstet Gynecol 92:44, 1968.

67. Thompson, H. E., Makowski, E. L.: Birth weight and gestational age. Obstet Gynecol 37:44, 1971.

68. Tulchinsky, D.: Endocrine evaluation in the diagnosis of intrauterine growth retardation. Clinical Obstetrics and Gynecology. Frigoletto, F. D. Jr., Guest Editor. (Hagerstown, MD: Harper & ROw, 1977).

69. Tulchinsky, D., Osanthanondh, R., Finn, A.: Dehydroepiandrosterone sulfate loading test in the diagnosis of complicated pregnancies. N Engl J Med 294:517, 1976.

70. Usher, R., McLean, F.: Intrauterine growth of live born caucasion infants at sea level: standars obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. J Pediatr 74:901, 1969.

71. Varma, T. R.: Prediction of fetal weight by ultrasound cephalometry. Australia New Zealand J Obstet Gynecol 14:83, 1974.

72. Vohr, B. R., Oh, W., Rosenfield, A. G., Cowett, R. M.: The preterm small-for-gestational age infant: A two year follow-up study. Am J Obstet Gynecol 133:425, 1979.

73. Yousem, H., Seitchik, J., Solomon, D.: Maternal estriol excretion and fetal dysmaturity. Obstet Gynecol 128:491, 1966.

74. Warkany, J., Monroe, B. B., Sutherland, B. S.: Intrauterine growth retardation. Am J Diseases of Children 102:127, 1961.

75. Warsof, S. L., Gohari, P., Berkowitz, R. L., Hobbins, J. C.: The estimation of fetal weight by computer-assisted analysis. Am J Obstet Gynecol 128-881, 1977.

76. Willcocks, J., Donald, I., Duggan, T. C., Day, N.: Foetal cephalometry by ultrasound. J Obstet Gynaec Br Comm 71:11, 1964.

77. Woodward, B., Pond, J. B., Warwick, R.: How safe is diagnostic sonar. Br J Radiology 43:719, 1970.

78. World Health Organization: Public health aspects of low birth weight. Third Report of the Expert Committee on Maternal and Child Health. WHO Tech Rep Serv 217:3, 1961.