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SYMPOSIUM ON 'NUTRITION AND THE FOETUS'

The assessment of foetal growth

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I must make it clear that the foetus I shall discuss is the only one of which I have any experience, the human foetus.

The foetus grows at an amazing rate. By the time of birth, a baby is six billion times heavier than the egg from which it came, whereas from birth to maturity weight increases only twenty times (Arey, 1965). If the baby continued to grow after birth, even at the reduced rate at which the foetus grows during the last month of pregnancy, the weight of the adult would be two trillion times that of the earth. Despite the dramatic rate of foetal growth and development, methods of assessing it objectively are very recent. Streeter (1920) and Scammon & Calkins (1929) produced tables of dimensions of foetuses of different ages measured at postmortem examinations and their work is classic, although necessarily limited. In more recent years there have been a number of investigations of large populations based on birth weight information. If large numbers of babies, born in different places, are to be studied, the results must be both simple and reliable. The two simple measurements which have been most widely used to establish the pattern of normal foetal growth are *birth weight* and *gestational age*, and these are the foundation of all the impressive growth charts from Lubchenco, Hansman, Dressler & Boyd (1963) onwards. It is not difficult to weigh babies at birth with a reasonable degree of accuracy, but the estimation of gestational age can be a difficult affair as we shall see later. Knowledge of gestational age is fundamental, a baby cannot be 'small for dates' unless we know what the dates are. Accurate estimation of maturity depends on meticulous antenatal care and it is essential for the mother to attend early in pregnancy so that the necessary information can be assembled. It is well to remember that although birth weight is a simple criterion there is a wide range of normal variation. After 32 weeks gestation it can be generalized that the smallest baby born at any given time is approximately half the weight of the heaviest baby born at that same time.

Thomson, Billewicz & Hytten (1968) studied birth weights in 52 000 cases in Aberdeen (1948-64) and found fewer anomalies than had been reported in other series, due to the care of the obstetricians in collecting information about last menstrual period, size of uterus in early pregnancy and date of foetal movement. Thomson *et al.* (1968) produced tables showing the effect of foetal sex and

maternal parity, height, weight and social class on birth weight. Birth weights by sex were practically identical at 32–33 weeks and then gradually diverged, males being 150 g heavier than females at term. Second and subsequent babies grew faster than first babies, the difference of about 100 g being fairly constant from 32 weeks of gestation onwards (perhaps because of better uterine circulation). As regards maternal size, the baby of a woman 170 cm tall weighing 75 kg was 750 g heavier than the baby of a woman 150 cm tall weighing 40 kg.

Gruenwald of Baltimore advanced the hypothesis that in most cases birth weight curves follow a linear course until 'growth support' begins to fail. The lower the level of 'growth support' the earlier the departure from the straight line and the lower the birth weight at term (Gruenwald, 1967).

High birth weight

Three main clinical groups are associated with high birth weight, which is usually defined as 4000 g or over. (1) Large mothers: perhaps good nutrition is an important factor in producing the larger individuals found in some highly developed societies (e.g., Scandinavia). (2) Prolonged pregnancy: 18% of babies weigh over 4000 g in cases of prolonged pregnancy (Beischer, Evans & Townsend, 1969). (3) Disturbance of carbohydrate metabolism: the association of large babies with diabetes is well known, but good diabetic control will keep foetal weight down. Of all hormones, foetal insulin may be chief regulator of growth.

The large baby has always posed technical problems to the obstetrician and is associated with increased risks to itself and to its mother, the chief ones being diabetes and dystokia. Hansmann & Hinckers (1974) emphasized the dangers associated with foetuses weighing more than 4000 g; if a large foetus is suspected, maternal glucose metabolism should be investigated and foetal size assessed by ultrasound. Elective Caesarean section should be considered when the baby is thought to be excessively large and evidence of disturbed glucose metabolism should be viewed as an indication for delivery before term.

Low birth weight

In *Practical Paediatric Problems*, Hutchison (1967) pointed out that 70% of neonatal deaths and 50% of stillbirths were associated with low birth weight. Thomson, *et al.* (1968) found that all babies weighing less than 5 lb (2270 g) at birth had high perinatal mortality rates, without any clear trend by gestational age.

Much attention has been given to low birth weight infants in recent years and particularly to those 'light for dates' infants who seem to be suffering from intrauterine growth retardation.

Thomson & Billewicz (1976) point out that intrauterine growth retardation cannot be diagnosed from birth weight and gestational age alone as these tell us nothing about the rates of growth in individual cases, some babies having attained their birth weight by uniform slow growth, others having had retardation of growth in late pregnancy only.

The basic cause of foetal growth retardation is malnutrition in some form or other. Malnutrition of the foetus can be secondary to maternal disease in pregnancy, as in pre-eclampsia, where the defect is probably a vascular one; it can also occur, from causes unknown, in apparently healthy well-nourished mothers when it is described as 'placental insufficiency'. In a world where so many are starving it seems likely that maternal malnutrition is the main cause of foetal growth retardation. Scientific proof of this assertion may be lacking because hungry people in poor countries are not usually the populations subjected to detailed statistical analysis. The situation in Holland in 1944–45 was exceptional: an acute famine occurred in an advanced western community as the result of war and much information has been collected subsequently (Stein, Susser, Saenger, *et al.* 1975). Retarded foetal growth was one of the effects reported. When surviving males were examined 19 years later, those who were exposed to famine during late pregnancy and the first months of life had lower rates of obesity than those who were exposed to famine in the first half of pregnancy only (Ravelli, Stein & Susser, 1976).

Dr J. P. Greenhill, in his farewell remarks in the 1975 Year Book of Obstetrics and Gynaecology, states that in 1921 when he was first resident at the Chicago Lying-in Hospital, there was a rule that women should not gain more than 15 lb in their entire pregnancy and a salt-free diet was prescribed. He believes some babies were small because of the severe restriction on the mother's weight.

Rush, Stein, Christakis & Susser (1974) stated that nutrition during pregnancy is very likely to have a strong effect on birth weight and set up a randomized double-blind trial of nutritional supplementation in a deprived American black population. In a similar study from rural Guatemala, Habicht, Yarbrough, Lechtig & Klein (1974) showed that the mean birth weight of infants rises with maternal energy intake in pregnancy irrespective of maternal age, parity, interval since last birth, length of gestation, illness during pregnancy or sex of the child.

Smoking as a cause of low birth weight has received much attention since the Second Report of the British Perinatal Mortality Survey (1966) which concluded that smoking in the latter part of pregnancy was harmful to normal growth and survival of foetus (Butler & Alberman, 1969). Later Butler & Goldstein (1973) found evidence of physical and mental retardation at the ages of 7 and 11 in children of mothers who smoked during pregnancy.

Cole, Hawkins & Roberts (1972) showed that smoking raises the level of carboxyhaemoglobin in the blood and that the foetal concentration of carboxyhaemoglobin was about twice that of the mother. Tanaka (1965) found an inverse correlation between the amount of carboxyhaemoglobin in maternal blood and the tissue respiratory rates of placental villi. Pettigrew, Logan & Willocks (1976) confirmed the increased incidence of low birth weight in closely matched pairs of smokers and non-smokers and found higher levels of cyanide and thiocyanate in the blood and urine of those mothers who smoked and in their foetuses; this may produce interference with vitamin B₁₂ metabolism. Rush (1974) suggested that the effects of smoking on foetal growth could be simply the result of

a reduced food intake during pregnancy and Davies, Gray, Ellwood & Abernethy (1976) suggested that more food during pregnancy to increase the weight gain in smoking mothers might prevent or at least reduce foetal growth retardation.

The risks of foetal growth retardation

The growth-retarded foetus faces a risk of intrauterine death. If born alive, the risk of death in the neonatal period is low but the child's mental ability may be retarded. This suspicion seemed to be confirmed by studies by McDonald (1965), Barker (1966) and Hockey & Hawks (1967) who all found evidence of an increased rate of mental retardation in children who had been 'small for dates' at birth.

More recent studies suggest that improved obstetric and paediatric management can reduce these risks. Rawlings, Reynolds, Stewart & Strang (1971) studied the progress of 68 infants born in 1966–69 at a weight of 1500 g or less and found normal results in 59 cases, which suggested that prognosis for infants of very low birth weight had improved with modern methods of care. Prevention of biochemical abnormalities such as hypoxia, hypoglycaemia and hyperbilirubinaemia has been particularly important. Rhodes (1973) stated that it is certain that obstetric practice can make a contribution to the reduction of the total amount of mental retardation. Davies & Stewart (1975), in an extensive review, reported an improvement in the prognosis for life and normal development of low birth weight infants born since 1960. In particular, there had been a reduction in the incidence of spastic diplegia and other major handicaps in centres specializing in modern methods of perinatal care. Davies & Stewart believe that remediable events around the time of birth are of greater importance in determining later handicap than is prenatally or genetically determined disease. Prolonged slow growth in utero seems to be followed by slow growth and development after birth, according to Fancourt, Campbell, Harvey & Norman (1976) who studied, at a mean age of 4 years, a group of 'small for dates' term babies whose intrauterine growth had been followed by serial ultrasonic cephalometry; the poorest development during infancy was recorded in those who had the earliest onset of growth failure in utero. Further studies are awaited to assess the full significance of this information.

Methods of studying the growth of the living foetus

(1) *Clinical*. This remains the basic method of study and may be the only method available. This is an age of complex tests, but all tests cannot be available everywhere, so it behoves us to keep our five clinical senses. The selection of patients for special investigation depends upon the care with which the clinician conducts routine antenatal examinations and the best results are obtained when the patient attends early in pregnancy. Features worthy of special note are: (a) obstetric history, previous 'light for dates' baby, previous stillbirth or neonatal death, or previous severe pre-eclampsia; (b) menstrual history, regularity, use of contraceptive pill, date of last menstrual period and accurate calculation of

expected date of delivery; (c) symptoms of pregnancy, including date of foetal movement; (d) abdominal and pelvic examination, to assess uterine size.

(2) *Biochemical*. Coyle & Brown (1963) demonstrated that maternal urinary oestriol excretion correlated with birth weight and Frandsen (1966) showed a marked correlation between oestriol excretion and the weight of the foetal adrenal.

Maternal urinary oestriol excretion has become the most widely employed biochemical test of foetal growth since automated methods (Ua Conaill & Muir, 1968; Barnard & Logan, 1970) have become available. Barnard & Logan (1972) assessed the value of urinary oestriol estimation in predicting dysmaturity: they found that single measurements were of little value but that the presence or absence of a rising trend in oestriol output was a more reliable index. Similar results were reported by Bergsjø, Bakke, Salamonsen, Støa & Thorsen (1973). Results can be correlated with creatinine excretion which obviates the difficulty of incomplete urine collections (Barnard & Logan, 1971). The determination of creatinine also allows the possibility of oestriol estimation from casual urine samples. Several workers (e.g., Masson, 1973) have recently proposed the use of plasma oestriol estimations, but results of large series are not available and the advantage of plasma over urine estimations is not yet clear.

The argument for using oestriol tests at all is that oestriol production is the result of unique biochemical cooperation between the foetus and placenta. But one must remember that there is a complex series of steps between the foetal adrenal at the start and the eventual production of oestriol in the urine and its analysis. A deficiency of foetal adrenal tissue and a deficiency of sulphatase in the placenta are two causes of low oestriol values. Others are drugs such as steroids given for asthma etc., meprobamate, ampicillin, mandelamine.

Human placental lactogen (HPL) is a protein hormone secreted exclusively by the placenta. It has been estimated in an attempt to correlate it with foetal weight but evidence is conflicting. HPL is known to be low in patients with hypertension and pre-eclampsia, but Spellacy, Buhi & Birk (1975) found that it did not help to predict intrauterine death in the absence of hypertension.

Enzymes. Numerous placental enzymes have been measured. Heat-stable alkaline phosphatase (HSAP) was promising but early work has not been confirmed.

Placental transfer tests (e.g., selenomethionine uptake, Garrow & Douglas, 1968) are attractive in theory but there is difficulty in achieving standardization and these techniques have not been widely used.

X-rays. Radiological examination has been used for many years to estimate foetal maturity but its use in studying foetal growth in an individual case is limited because of the health hazard involved. None the less, there are some characteristic X-ray signs of intrauterine growth retardation; these are: (a) delayed maturation of bones, (b) oligohydramnios, (c) hyperflexion of foetus.

Diagnostic ultrasound (sonar) offers the only method by which repeated direct measurements can be made on the same foetus during intrauterine life and is uniquely valuable in the estimation of foetal growth. This work originated in

Glasgow under the direction of Professor Ian Donald. Serial foetal cephalometry was first described as a test for foetal growth by Willocks (1962). The biparietal diameter of the foetal skull was found to correlate with foetal weight and (rather less well) with gestational age. A reduced rate of biparietal growth in dysmature babies was shown in 1967 and the use of serial cephalometry in association with oestriols was described. Campbell (1969) improved the technique of cephalometry and has followed this work in numerous publications. A recent review of the subject appears in Campbell (1976).

I referred earlier to the importance of dating a pregnancy to know the gestational age. Great accuracy has been achieved in this due to the work of Robinson (1972, 1973) who has devised methods of measuring crown-rump length and detecting foetal heart action in the early weeks of pregnancy.

Other ultrasonic measurements have recently been investigated in the hope of producing more refined assessment of foetal growth. Garrett & Robinson (1971) measured cross-sectional areas of the foetal head and trunk. Campbell & Wilkin (1975) measured foetal abdominal circumference and concluded that the best method for screening out the 'small for dates' foetus would be to use an early scan for foetal maturity combined with a late measurement of foetal size, e.g., an embryonic crown-rump length between 6 and 12 weeks and a late measurement of foetal abdomen circumference between 32 and 36 weeks. Higginbottom, Slater, Porter & Whitfield (1975) also considered that ultrasonic measurement of foetal trunk circumference was of clinical value. Lunt & Chard (1976) concluded that the 'skull and thoracic areas multiple (STAM)' index is a more efficient predictor of birth weight than the biparietal diameter.

While recognizing the possible significance of newer techniques of foetal growth measurement and exploring their potential, the methods employed in our own hospital for studying foetal growth are serial ultrasonic cephalometry and serial oestriol excretion measurement. This combination of tests has now been well tried by many years of clinical practice and has stood favourable comparison with other methods (Robinson, Chatfield, Logan, Tweedie & Barnard, 1973; Robinson, Chatfield, Logan & Hall, 1974).

The ideal solution to the problem of foetal growth retardation would probably be to provide some form of intrauterine nutrition until the child is big enough to survive. As this solution remains speculative, the practical approach we adopt to the problem is to terminate the pregnancy in the foetal interest when there is firm evidence of failing growth, while avoiding unnecessary and premature obstetrical intervention in doubtful cases.

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