SCREENING FOR THE SMALL-FOR-DATES FETUS WITH ULTRASOUND

by

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DECLARATION

The large majority of ultrasound measurements described in the studies reported in this thesis were performed by myself. Those not carried out by myself were performed by my colleague, Dr. S.P. Munjanja, initially under my supervision.

This thesis has been composed by myself and has not previously been submitted for any degree at this or any other University.

James P. Neilson
June 1984
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INTRODUCTION

This thesis describes evaluation of a technique for screening for the small-for-dates fetus using diagnostic ultrasound. The studies were all performed in the Queen Mother's Hospital, Glasgow.

The study reported in Chapter 3 ("Development of a means for screening for the small-for-dates fetus using a two-stage ultrasound examination schedule") has been previously published (Neilson et al., 1980) as have the findings in twin pregnancies described in Chapter 6 (Neilson 1981, 1982). The other studies have not, as yet, been published.

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ABSTRACT

To minimise the hazards of fetal growth retardation by optimal perinatal management, the small-for-dates fetus must be detected antenatally. However, because the detection rate during routine antenatal care is usually less than 50 %, a technique for screening for the small-for-dates fetus appears highly desirable. Diagnostic ultrasound would appear the ideal tool for this.

A two-stage ultrasound examination schedule has been evaluated as a procedure for screening for the small-for-dates fetus. The first examination comprises accurate assessment of gestational age, in early pregnancy, with which to interpret the results of the second (assessment of fetal size) at the chosen screening period of between 34 and 36 weeks. To assess the best measurement at this latter examination, seven different fetal parameters were measured, and later compared, in a study of 474 largely unselected patients. Trunk measurements were more effective than head measurements. Trunk area and trunk circumference were very highly correlated ($r = 0.995$) and were similarly effective. The product of two of the parameters, crown-rump length and trunk area, (CRL X TA) which was found to have a sensitivity of 94 % and a specificity of 88 %, was selected for further study as the second-stage examination.

Prospective evaluation of 877 low risk and 201 high risk patients confirmed the effectiveness of CRL X TA measurement with sensitivities of 94 % and 92 % respectively. In all, 93 % of 122 single and 100 % of 19 twin small-for-dates babies were detected in advance by CRL X TA measurement. Analysis of pooled results confirmed better sensitivity by CRL X TA compared with TA alone ($p < 0.001$)

The two stage schedule is suitable as a screening technique because it is simple, quick to perform and highly effective. A prospective randomised controlled trial was performed on the 877 low risk patients to assess the impact of screening. No advantage could be dempnstrated. CRL x TA measurement is recommended in any patient in whom there is any reason, however minor, to suspect that the fetus may be small-for-dates. It cannot be recommended as a general screening technique.

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CHAPTER 1.

REVIEW OF THE LITERATURE

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1: FACTORS INFLUENCING THE RATE OF FETAL GROWTH:

Introduction

Ethnic factors

Altitude

Maternal factors

Fetal factors

Multiple pregnancy

Familial factors

Utero-placental insufficiency

INTRODUCTION

In an address to the Edinburgh Obstetrical Society in 1902, Ballantyne stated that "neither fetal size nor weight can be regarded as sure indications of fetal age" (Ballantyne, 1902). Few others possessed his insight and understanding and, for much of this century, all babies of low birthweight have been classified as "premature", the easily quantifiable index of weight being more attractive than the, often uncertain, index of gestational age. However, writing in 1947, McBurney states,

> "Most obstetricians are able to recognise the 'presumptive signs' of pregnancy. These findings accompanying a two month period of amenorrhoea, should assure the physician of being reasonably correct in diagnosing a pregnancy of six to eight weeks duration. In such instances, when the patient has been delivered of her baby within one or two weeks of, or even after the estimated date of parturition, it is extremely annoying to have a paediatrician insist that the baby is premature because it may weigh only four and one-half or five pounds."

He went on to state that such babies were malnourished in utero and that this might be due to a small placenta or to disturbance of the placental circulation, and that the undernourishment might be sufficiently severe as to cause intrauterine death (McBurney, 1947). Clifford, writing a few years later, classified the clinical features associated with postmaturity; he included, amongst his case reports, babies of low birthweight born after 300 days gestational age. The associated findings of apparent recent weight loss and meconium staining, he attributed to placental dysfunction (Clifford, 1954). Further important studies, such as those of Warkany et al (1961) and of Gruenwald (1963) which described, respectively, the clinical and pathological features associated with retarded fetal growth, aided wider appreciation of the differences between low birthweight preterm infant and the low birthweight term infant.

As a result, accepted definitions have changed. Babies weighing less than, or equal to, 2500 grams are classified as "low birthweight infants" and not, as formerly "premature." Babies born after less than 259 days (37 weeks) of pregnancy are defined as "pre-term infants", those born between 259 and 293 days (37 to 41 weeks) as

"term infants" and those born after 294 days (42 weeks) as "post-term infants" (Ounsted and Ounsted, 1973). Definitions of "light-for-dates infants (also called "small-for-gestational age" or "small-for-dates") vary according to different authors. These definitions include birthweight equal to or less than the 5th or 10th percentiles or minus 2 standard deviations below the mean for length of gestation according to established birthweight charts (e.g. Lubchenco et al., 1963; Thomson et al., 1968; Usher and McLean, 1969; Babson et al, 1970; Milner and Richards, 1974). Around one-third of low birthweight infants are not pre-term but are small-for-dates (Gruenwald, 1963). The term "dysmature", which has been used as synonymous with "small-for-dates", is misleading and will not be used in this thesis. The terms "intrauterine (or fetal) growth retardation" are more difficult to define since they do not strictly speaking rely for classification on quantifiable indices such as age or weight. This matter will be discussed in detail later.

On reviewing the literature on factors which influence the rate of fetal growth, it is apparent that many reports fail to distinguish adequately between the pre-term and small-for-dates groups which constitute the low birthweight population. Some reports were published before widespread acceptance of the new definitions, and others were compiled in communities in which reliable information about gestational age was unobtainable. Thus, many of the factors described in the following discussion should be seen as possible, rather than definite, influences on the rate of fetal growth.

ETHNIC FACTORS

Extensive data obtained in a World Health Organization study of birthweight throughout the world, has shown that the average duration of pregnancy in all cultures is constant (Rosa and Turshen, 1970). Despite this, the variation in mean birthweight may be substantial. Meredith (1970) reviewed more than 270 studies of birthweights which were carried out between 1945 and 1966. The smallest neonates are those of the Lumi tribe of New Guinea who inhabit the Toricelli Mountains at an altitude of 1700 feet. Their babies have a mean

birthweight of 2.40 kg (Wark and Malcolm 1969). The largest babies are born on the Carribean Islands of Nevis and Anguilla, where the mean birthweight is 3.88 kg (Ashcroft et al., 1966). Almost as heavy are the infants of the Cheyenne tribe of the USA: the mean birthweight is 3.83 kg, compared with a mean of 3.32 kg for the Caucasian population of the USA (Meredith, 1970). It is difficult to separate socio-economic and ethnic factors in explaining cross-cultural variation in birthweight. The Lumi people, for example, were completely isolated from the outside world until after the second world war; they live a primitive existence on a staple diet of sago and leaves, supplemented occasionally by birds and rodents (Wark and Malcolm, 1969). The inhabitants of Nevis and Anguilla are predominantly of West African origin, their ancestors having been transported to the West Indies as slaves during the 17th and 18th centuries; the mean birthweight amongst the islanders is 800g greater than that of the indigenous population of West Africa (Meredith, 1970).

The relative importance of ethnic factors in influencing birthweight variation is of relevance in Britain because of the now substantial immigrant Asian population. Studies in London (Grundy et al., 1978) and in Leicester (MacVicar, 1981) have demonstrated a difference of 300g in mean birthweight between Asian and white populations. However, the influence of this on fetal risk is, as yet, uncertain (British Medical Journal, 1978). Certainly in the Leicester series there was a three-fold greater perinatal mortality rate amongst small-for-dates Asian infants than their white counterparts using identical criteria but different birthweight charts to define each group. (MacVicar, 1981).

ALTITUDE

Babies born at high altitude are of lower birthweight than those born at sea-level. The mean birthweight in Lake county, Colorado, at an altitude of 10,000 feet, is 2.66 kg (Lichty et al., 1957); this is the lowest mean birthweight recorded in a Caucasian population and it is virtually identical to the mean birthweight amongst Pygmies (Meredith, 1970). The lowering of birthweight at altitude does not

appear to be due to a higher incidence of pre-term delivery or of congenital abnormality (Lichty et al., 1957), and both body length and head size of the neonates are reduced (Howard et al., 1957a). Neither arterial oxygen saturation nor haematocrit levels in neonates in Lake County, differed from accepted values at sea-level to indicate chronic fetal hypoxia as the cause of reduced growth (Howard et al., 1957b). Kruger and Arias-Stella (1970) likewise found reduced birthweight in babies born at Rio Pallanga, 15,000 feet up in the Peruvian Andes. However, whilst mean birthweight was 544g less in Rio Pallanga than in Lima, at sea-level, the mean placental weight at high altitude was 60g greater, suggesting a compensatory mechanism adapted to the hypoxic environment. Similar findings have been noted in sheep raised at high altitude (Alexander, 1978). Sobrevilla et al. (1968) found reduced mean birthweight in a small group of infants delivered at an altitude of 13,000 feet in the Andes, although they also noted reduced placental weight. These authors also found oestriol excretion to be reduced in pregnancy at high altitude despite good fetal outcome. Small term babies born at high altitude show the same signs of behavioural immaturity in interactive and motor abilities as do small-for-dates neonates born at sea-level (Saco-Pollitt, 1981). It should be noted in passing that the widely-used birthweight chart of Lubchenco et al. (1963) was compiled from data obtained in Denver, Colorado, at an altitude of 5,000 feet above sea-level.

MATERNAL FACTORS

Mean birthweight is lower among babies born to mothers of lower social class (Baird, 1963; Thomson et al., 1968; Rosa and Turshen, 1970). There is a large cluster of factors which may explain this, including poor housing, nourishment and health, and maternal smoking. To quote Ounsted and Ounsted (1973):

> "in a society such as our own, in which social class tends to be inconsistant in a given biography, variable within a family and markedly unstable over the generations, we think it a doubtful measure in biological studies."

Larger mothers tend to have larger babies. Thomson et al. (1968) found that the babies of women 170 cms tall and weighing 75 kgs will be 750g heavier, on average, than those of women who are 150 cms tall

and weigh 40 kg. Parity also influences the rate of fetal growth: second and subsequent babies grow faster than first-born (Thomson et al., 1968).

The relationship of maternal nutritional status to the rate of growth of the fetus has been extensively studied. There is no clear evidence, in developed countries, of improved outcome of pregnancy by dietary supplementation (Rosa and Turshen, 1970). Beal (1971) studied a group of white, middle class American women and found no significant correlation between carbohydrate, fat, protein or calorific intake during pregnancy, and birthweight. Adverse fetal outcome was noted in a large trial of high protein supplementation during pregnancy in New York (Rush et al., 1980). Thomson (1957) and Baird (1963) have suggested that the woman's life experience of nutrition is of more importance to her reproductive capacity than dietary intake during pregnancy. Studies carried out during times of war and in developing countries have, however, indicated a relationship between maternal nutritional status and fetal growth rate. The mean birthweight of Japanese infants fell by 200g in the immediate post-war period, although there was no change in mean gestational age (Gruenwald et al., 1967). There was a similar fall in birthweight (240g) in Rotterdam and the Hague, between September 1944 and May 1945, when a general strike resulted in widespread malnutrition (Smith, 1947). During the seige of Leningrad in 1941, half of all babies weighed less than 2.5 kg, this being attributed to both pre-term delivery and fetal growth retardation (Antonov, 1947). This was accompanied by a stillbirth rate of 5.6% (unlike Holland where there was no increase in stillbirths). The conditions in Leningrad were more extreme than in Holland and Antonov stressed the probable additional influences of stress, physical exertion and cold on poor reproductive outcome. Both Dutch and Russian papers note prevalent amenorrhoea. Halbicht et al. (1974) have reported increased birthweight by dietary supplementation of pregnant women in poor Guatemalan villages where there is dietary, biochemical and anthropometric evidence of protein deficiency. After calorific supplementation was initiated there was a 40% decrease in the incidence of low birthweight infants. This effect was not due to a decrease in the rate of pre-term delivery.

Exposure of the mother to various agents may result in inpairment of fetal growth rate. The most widely recognised of these agents is the cigarette (Lancet, 1979), the mean birthweight of babies born to smoking mothers being reduced by around 200g (Underwood et al., 1967; Andrews and McGarry, 1972). It has been hypothesised that this effect may be due to decreased nutritional intake in smoking mothers but this was not confirmed by large studies in Canada (Meyer, 1978; Haworth et al., 1980). The impairment of fetal growth rate is probably a direct effect. Circulating carboxyhaemoglobin levels are higher in fetuses of mothers who smoke, and this results in a shift to the left of the oxygen dissociation curve with consequent reduced availability of oxygen to fetal tissues (Cole et al., 1972). Other agents also appear harmful. More than 30% of infants born to chronically alcoholic mothers are small-for-dates (Jones et al., 1974). Stone et al. (1971) reported on 382 pregnant heroin addicts. Almost half of their infants were of low birthweight, 40% of these being born after 38 weeks. Heroin is of low molecular weight and crosses the placenta and may, itself,inhibit fetal growth although these mothers, like the alcoholics, tend to show signs of multiple self deprivation and abuse. Prescribed drugs have not been found blameless. Warrell and Taylor (1968) reported a high incidence of small-for-dates infants born to mothers on corticosteroid therapy throughout pregnancy, when compared with women with similar illnesses but not taking steroid medication.

Maternal disease may also influence fetal growth rate. The best recognised condition is hypertensive disease - both essential hypertension and pre-eclampsia. The 1958 British Perinatal Mortality Survey found the increased incidence of small-for-dates infants to be confined to those mothers with severe hypertensive disease (Butler and Alberman 1969). De Souza et al., (1976) found no lowering of mean birthweight in pre-eclamptics, although Gruenwald (1966b) showed that while there was a higher incidence of small-for-dates infants born to hypertensive mothers, an excessive number of high birthweight infants resulted in an approximation to the overall mean. Maternal diabetes mellitus, whilst more characterically associated with excessive fetal growth, may also impair intrauterine growth rate (Naeye, 1965; Gruenwald,

1966b) when microangiopathy exists (Persson, 1974). In some parts of the world, malaria may be implicated in reducing fetal growth; Cannon (1958) showed that in 37% of cases in which the placenta showed signs of malarial infection, the baby weighed less than 2.5 kg at birth. The relative proportions of pre-term and small-for-dates infants were not specified.

Following their experiments on crossing Shetland ponies and Shire horses, Walton and Hammond (1938) proposed the concept of a maternal regulator which determined fetal growth rate. This provided an explanation for their findings that foals born to Shetland mares by Shire stallions were of similar birthweight to pure Shetlands, and that the foals of Shire mares by Shetland sires were similar in weight to pedigree Shires. Ounsted and Ounsted (1966) have suggested that the same mechanism exists in humans and that the rate of intrauterine growth is principally determined, under physiological conditions, by two factors : the pre-determined setting of the maternal regulator, and antigenic dissimilarity between mother and fetus. The maternal regulator, the nature of which is uncertain (Ounsted, 1965), would account for the persistent production of small-for-dates infants by some women who have no disease process to account for this. Extensive pedigree studies have shown that this effect is transmitted through women only (Ounsted and Ounsted, 1968). Evidence that antigenic dissimilarity influences fetal growth rate has been provided by the study of birthweight in mixed-sex multiple pregnancies (Ounsted and Ounsted, 1970) on the assumption that the presence of the Y chromosome in a male fetus provides per se greater antigenic disparity with the mother than if the fetus were female. This challenges the concept of genetic (Cheek et al., 1977) or hormonal influences resulting in the greater birthweight of male infants (Lubchenco et al., 1963; Thomson et al., 1968; Usher and McLean, 1969; Babson et al., 1970; Milner and Richards, 1974).

FETAL FACTORS

Various fetal anomalies are associated with low birthweight for gestational age. Those include renal agenesis (Potter, 1965), trisomy 18 (Warkany et al., 1964; Lubchenco, 1970), trisomy 21 (Lubchenco,1970),

the de Lange syndrome (Silver, 1974), various forms of congenital dwarfism (Black, 1961), osteogenesis imperfecta (Lubchenco, 1970) and anencephaly, even allowing for the absence of skull and brain (Liggins, 1974). Naeye (1965b) has reported impaired fetal growth associated with congenital cardiac malformations, the small size of these infants being typified by reduced cell number in various organs; Davis (1967) has shown reduced birthweight in infants with Fallot's tetralogy. In contrast, Mehrizi and Drash (1961) found no essential difference in birthweight between babies with both cyanotic and acyanotic congential heart disease and controls, except that infants with transposition of the great vessels had a higher mean birthweight. The mechanism or mechanisms by which intrauterine growth rate if reduced in association with anomalous development is often uncertain and may vary with different conditions. The cause of intrauterine death and fetal growth retardation in renal agenesis is, for example, uncertain (Potter,1965); the operation of bilateral nephrectomy on fetal lambs will impair subsequent intrauterine growth without affecting plasma urea and electrolyte concentrations (Thorburn, 1974). Reduced intrauterine growth in anencephalics may be due to absence or deficiency of the pituitary gland (Liggins, 1974). It is generally accepted, however, that in most cases of fetal abnormality, both anomalous development and impaired growth are independant effects of a common cause. Spiers (1982) has put forward the hypothesis that intrauterine growth retardation predisposes the fetus to congenital malformation, but the evidence for this is unconvincing.

Some prenatal infections may impair fetal growth, including rubella (Naeye and Blanc, 1965; Lubchenco, 1970), syphilis, toxoplasmosis and cytomegalic virus (Ounsted and Ounsted, 1973). The most prominent of these, rubella, is associated with reduced cell number in the affected fetuses (Naeye and Blanc, 1965).

The role of the fetal endocrine organs in regulating intrauterine growth in the human is largely unclear. As has been discussed in the context of anencephaly, absence or deficiency of the pituitary gland appears to cause modest impairment of fetal growth. However, four reported cases of isolated primary pituitary hypoplasia, or aplasia,

related to babies of normal birthweight (Liggins, 1974). Babies with either familial growth hormone deficiency or pituitary dwarfism with high levels of inactive growth hormone, are usually of normal birthweight (Laron and Pertzelan, 1969), as are infants with congenital adrenal hypoplasia (Liggins, 1974). Thyroid hormone appears essential for normal intrauterine growth in the sheep and Rhesus monkey, as has been demonstrated by fetal thyroidectomy studies. Growth retardation is not, however, generally evident in the athyroid human neonate; there appears to be inter-species differences in the ease with which maternal thyroxine will cross the placenta (Thorburn, 1974). In contrast to other hormones, insulin does seem to have an important role in regulating growth of the human fetus. Hypoinsulinism resulting from congenital diabetes mellitus leads to marked impairment of fetal growth rate (Scott, 1966; Liggins, 1974).

Immunological factors may influence intrauterine growth (Scott, 1966). That greater antigenic dissimilarity with the mother may help account for the greater birthweight of male infants (Ounsted and Ounsted, 1970) has already been discussed. At least one tissue-specific autoimmune disease (Grave's disease) may, when present in a pregnant woman, be associated with impaired fetal growth (Jones, 1979). A proportion of those small-for-dates infants in whom there is no apparent explanation for impaired intrauterine growth show abnormal immunoglobulin profiles in their serum; whether this is due to sub-clinical intrauterine infection or to a primary immunological mechanism is uncertain (Jones, 1968).

MULTIPLE PREGNANCY

Babies born from multiple pregnancies tend to be smaller than singleton neonates of similar gestational age. Gruenwald (1966a, 1974) has suggested that human fetal growth would follow a linear path throughout the second and third trimesters of pregnancy were it not for impairment of nutritional supply to the fetus. In reality, departure from the hypothetical straight-line growth curve occurs at varying gestational age depending on the population studied. This flattening of growth rate occurs late in pregnancy in Sweden, for

example, and earlier in less affluent countries; it occurs earlier still in multiple pregnancies. Thus, in Birmingham, McKeown and Record (1952) found that whilst deceleration of growth rate in singleton pregnancies occurred at around 36 weeks, the same effect was seen in twin pregnancies at about 30 weeks, and in triplet and quadruplet pregnancies at 27 and 26 weeks respectively. Birthweight studies of twins in other populations have shown similar findings, with deceleration of growth rate occurring at between 29 and 33 weeks (Gruenwald, 1966b; Naeye et al., 1966; Daw and Walker, 1975; Bleker et al., 1979). The clinical significance of this phenomenon will be discussed in Chapter 6.

UTERO-PLACENTAL INSUFFICIENCY

Placental weight correlates well with infant birthweight, and this has led to the suggestion that the size of the placenta determines the growth rate of the fetus. This is unlikely to be true as it would imply that the placenta normally functions near the limits of its capacity, and there is no reason to think this; after all, a fetus may survive after 50% of the placental surface area has separated from the uterine wall with placental abruption. Both the fetus and placenta are components of the conceptus and it is more likely that the growth of both are regulated by the same mechanisms, or that the fetus regulates the size of the placenta as it does the growth of its internal organs (Gruenwald, 1974). Some workers have found an increased incidence of impaired fetal growth associated with placenta praevia (Varma, 1972; Neri et al., 1980), perhaps due to the unfavourable site of implantation or due to fibrosis following repeated bleeding episodes. Others have not found this association (e.g. Gabert, 1971). There have been claims that marginal and velamentous insertion of the umbilical cord may predispose to poor fetal growth, but this has not been demonstrated in recent studies (Uyanwah-Akpom and Fox, 1977; Woods and Malan, 1978). Placental infarction limits the area available for transfer between fetal and maternal circulations, but infarction results from changes in maternal blood vessels which supply the placental bed and it is not an example of primary pathology of the placenta. There is, at present, little to suggest that primary impairment of placental exchange

mechanisms is an important cause of retarded fetal growth (Cheek et al., 1977); of more importance seems to be the adequacy of the maternal blood flow to the placental intervillous space. For these reasons, the term "utero-placental insufficiency" is preferred to "placental insufficiency." Severe utero-placental insufficiency results in impaired transfer of oxygen, as well as nutrients, to the fetus, with consequent fetal asphyxia and death; when less severe, fetal growth will be restricted (Parer, 1976). This probably results from the lack of nutrition per se, but an alternative hypothesis is that an unknown placental-fetal factor causes impaired growth as a compensatory mechanism because unrestricted fetal growth in the presence of compromised utero-placental blood flow would lead to accelerated exhaustion of available oxygen and nutrients with the risk of fetal death (Vorherr, 1982).

In animal experiments it is possible to reduce maternal blood flow to the placenta by a variety of techniques (Dawes, 1976). Wigglesworth (1964), for example, ligated the blood vessels of one uterine horn in pregnant rats. Many of the conceptuses in the experimental horns died after the operation and the surviving fetuses showed varying degrees of stunting. There were differences in the degree of growth retardation of different organs in the survivors, the growth of the liver being more, and that of the brain less, retarded than the body as a whole - this is similar to the pathological findings demonstrated in human small-for-dates infants and will be discussed further on page 47. Sheppard and Bonnar (1976) studied the ultrastructure of the arterial supply of the human placenta in cases of severe fetal growth retardation and found occlusive atheromatous lesions with considerable fibrin deposition in all cases, whether or not the pregnancies had been complicated by maternal hypertension. This would account for reduced blood flow to the intervillous space. However, other workers (Brosens et al., 1977; De Wolf et al., 1980) have found these changes to be uncommon when fetal growth retardation has not been associated with overt maternal vascular disease.

It has been postulated that the balance between the effects of the prostanoids, prostacyclin and thromboxane A2, may serve as an important physiological mechanism in the local control of regional, including utero-placental, blood flow. Thromboxane A2 stimulates platelet aggregation and causes vasoconstriction, and its production by

activated platelets is enhanced in normotensive and hypertensive pregnancies associated with retarded fetal growth (Wallenburg and Rotmans, 1982). Prostacyclin, in contrast, is a strong vasodilator and the most potent inhibitor of platelet aggregation known. Production of prostacyclin by trophoblast is decreased in cases of fetal growth retardation (Jogee et al., 1983). These two effects, acting together, may account for the increased tendency to platelet aggregation in spiral arteries (Sheppard and Bonnar, 1981) and the decreased platelet lifespan (Wallenburg and Van Kessel, 1979) observed in such pregnancies. There is no evidence of disseminated, rather than local, intravascular coagulation in pregnancies complicated by fetal growth retardation in the absence of severe pre-eclampsia (Howie et al, 1971; Elder and Myatt, 1976). Other haematological and haemorheological features have been described in pregnancies which result in a small-for-dates infant. These include reduced plasma volume (Hytten and Paintin, 1963; Arias, 1975) and increased blood viscosity due to decreased erythrocyte deformability (Thorburn et al., 1982).

Whilst more knowledge is being gained about the pathophysiology of utero-placental insufficiency, the cause, in the absence of maternal vascular disease, is unknown.

2: CLINICAL SIGNIFICANCE OF BEING SMALL-FOR-DATES:

Introduction

Perinatal Mortality

Perinatal Asphyxia

Fetal Malformation

Long Term Sequelae

INTRODUCTION

In the preceding discussion, the many factors which can influence intrauterine growth rate and thus lead to the delivery of a small-for-dates infant have been described. Such infants are, as a group, more at risk of certain perinatal problems than are those that are appropriately grown, although the risks applicable to the individual small-for-dates fetus vary in degree and nature according to the aetiological background. While the high risk status of the small-for-dates group is substantiated by many publications there is no universally accepted definition of what constitutes a small-for-dates infant and, still less, of what constitutes fetal growth retardation.

Definition of small-for-dates (or more accurately light-for-dates*) relies on reference to a chart which plots birthweight against gestational age at delivery. Various such charts have been compiled. One of the earliest, and probably the most widely used, was constructed in Denver, Colorado, from the birthweight data of 5,635 liveborn infants (Lubchenco et al., 1963). The 10th percentile curve was used to differentiate small-for-dates from appropriately grown infants (Battaglia and Lubchenco, 1967). Thomson and colleagues published, in 1968, the results of a study of the birthweight of 52,000 singleton infants in Aberdeen (Thomson et al., 1968). Careful attention was paid to assessment of gestational age and this chart has been widely used in the United Kingdom and elsewhere, and extensively used in obstetric ultrasound research; both the 5th and 10th percentiles have been used as demarcation lines, and the Aberdeen chart also permits allowance for the effects of sex and parity in influencing birthweight. Usher and McLean (1969) have compiled a chart based on Montreal births; these authors advocate the more stringent definition of small-for-dates as birthweight below minus 2 standard deviations from the mean. Many other charts have been compiled and details vary with the populations studied.

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* To correspond to conventional obstetric terminology in the United Kingdom, the term "small-for-dates" is used in this thesis.

The risk of perinatal damage to small-for-dates fetuses will likewise vary according to the definition employed.

There are, however, limitations in defining impaired intrauterine growth in terms of birthweight for gestational age. Some fetuses may cease to grow at a sufficiently late stage in pregnancy that their subsequent birthweight is not so low as to include them in the small-for-dates category although they have clearly failed to achieve their genetic growth potential. Miller and Hassanein (1971), in response to this problem, have attempted to improve detection of impaired intrauterine growth by measurement of the dimensions of the newborn to assess nutritional status by calculation of the Ponderal index. Turner (1971) used a novel approach in comparing birthweights of infants with those of their siblings. She found normal variation in birthweight within sibship to be in the order of $\pm$ 10%. Study of infants with rubella embryopathy showed that 80% had birthweights outside this range although only about half of these would have been classified as small-for-dates by conventional standards. This approach, obviously applicable only to the offspring of multiparous mothers, could be used more widely to study impaired fetal growth due to utero-placental insufficiency although the fact that this problem tends to be recurrent would pose some difficulty. Certainly it is unclear what is the clinical significance of impaired fetal growth which either occurs so late in pregnancy or is of such a mild degree as not to "deflect" the fetus into the small-for-dates zone.

In the following discussion of the risks of fetal growth retardation, attention centres on the outcome for small-for-dates fetuses.

PERINATAL MORTALITY

Perinatal (especially intrauterine) death is an important risk of being small-for-dates. The Scottish Perinatal Mortality Survey for 1977, which assessed all perinatal deaths in the country during that year, showed that 116 deaths in singleton pregnancies (11%) occurred in small-for-dates babies in the absence of fetal abnormality, maternal

disease and other complications of pregnancy (McIlwaine et al., 1969b); 80% of these deaths occurred in utero. A study in Melbourne of 500 consecutive small-for-dates babies likewise demonstrated a raised perinatal mortality rate : 5.2% compared with 1.2% in appropriately grown controls (Dobson et al., 1981). The perinatal mortality rate was 8.5 times greater in those infants whose birthweight was less than the 5th percentile for gestational age than those whose birthweight fell between 5th and 10th percentiles (19% against 2.2%); this was in part due to an increased incidence of major abnormality in the very small babies. Lugo and Cassidy (1971), in Alabama, found that, when babies of birthweight less than 1 kg are excluded, the perinatal mortality rate among small-for-dates babies (almost 10%) is equivalent to that of pre-term infants. In a review of perinatal mortality in Montreal, Usher (1971) found the mean gestational age at the time of intrauterine death among small-for-dates fetuses to be 37 weeks with all deaths occurring after 32 weeks; he felt that most of the deaths were potentially preventable by early recognition of fetal growth retardation and planned early delivery. Similarly, the Scottish Perinatal Mortality Survey demonstrated that 45% of intrauterine deaths among small-for-dates fetuses occurred after the 36th week (McIlwaine et al., 1979b). Death is usually due to asphyxia resulting from utero-placental insufficiency, although fetal malformation also makes a significant contribution.

PERINATAL ASPHYXIA

There are two main reasons why perinatal asphyxia is more common among small-for-dates fetuses : firstly, uterine contractions exacerbate the utero-placental insufficiency and secondly, as a consequence of intrauterine malnutrition, the small-for-dates fetus has less metabolic reserve to withstand the hypoxic stress of labour. In addition, the umbilical vessels may be more vulnerable to compression during labour because the amniotic fluid volume is often reduced and Wharton's jelly decreased in amount. Low et al., (1972) found that almost half of the small-for-dates fetuses in their series had moderate or severe metabolic acidosis at delivery; intrapartum asphyxia was more common when labour was pre-term (83% incidence). Perry et al.,

(1976) also found an increased incidence of low Apgar scores among small-for-dates fetuses, with a higher incidence after pre-term than term labour. Dobson et al., (1981) quoted a 13% incidence of fetal asphyxia (defined as an Apgar score of less than 5 at one minute) among small-for-dates infants with birthweights less than the 5th percentile; both those with birthweights between 5th and 10th percentiles and normally grown controls had a 7% incidence of fetal asphyxia. Lin et al., (1980) studied 37 small-for-dates and 108 appropriately grown fetuses during labour. In the absence of decelerations on continuous fetal heart rate tracings there was no difference in acid-base status between the two groups. Late decelerations were, however, more common in the small-for-dates group (30% incidence compared to 7% in controls). Small-for-dates fetuses that did develop heart rate decelerations were more likely to develop lactic acidosis than were normally grown babies, indicating diminished metabolic reserve.

NEONATAL PROBLEMS

Neonatal morbidity encountered by small-for-dates infants may conveniently be divided into three categories:

(i) related to fetal factors, such as chromosomal abnormalities, congenital infections and other malformations;

(ii) related to intrapartum asphyxia, such as meconium aspiration syndrome, hyperviscosity and post-asphyxia encephalopathy;

(iii) related to abnormalities of substrate transfer and aberrations of hormonal control, such as neonatal hypoglycaemia and hypocalcaemia. (Oh, 1977).

Neonatal hypoglycaemia is of particular interest because it is not uncommon, it is easily treated if recognised (Neligen et al., 1963), and it may account in part for the high prevalence of long term neurological impairment noted in early studies of the postnatal development of small-for-dates infants. Hypoglycaemia results from the decreased stores of glycogen which follow intrauterine malnutrition, and may be avoided by the early feeding of small-for-dates infants (Rabor et al., 1968).

FETAL MALFORMATIONS

Fetal malformation is not a consequence of intrauterine growth retardation but it has a higher incidence among small-for-dates babies and this has been discussed earlier in this chapter. In their series Dobson et al., (1981) found an incidence of 17% of major malformation among small-for-dates infants with birthweights less than the 5th percentile.

LONG-TERM SEQUELAE

Reports on post-natal growth of small-for-dates infants have described different findings. Fitzhardinge and Steven (1972a) followed up 96 infants that were severely growth retarded at term, until between 4 and 6 years of age. After initial catch-up growth, from below the 3rd percentile at birth to between the 10th and 25th percentiles at six months, the mean height and weight of the group remained in the same low percentile band. A more recent study of postnatal growth of 47 small-for-dates infants (Davies and Beverley, 1979) showed no significant difference from normal birthweight controls when assessed at 12 months of age. Post-natal growth of small-for-dates infants will be discussed further in Chapter 2.

The effects of fetal growth retardation on ultimate neorological and intellectual competence are obviously of considerable importance Animal experiments have shown that the developing brain is most vulnerable to the effects of malnutrition at the time of its fastest growth (Dobbing and Sands, 1970). This brain growth spurt runs from about mid-pregnancy to about 18 months of postnatal age in the human (Dobbing, 1974). Dobbing has predicted that when growth retardation only occurs during the third trimester and is followed by good catch-up growth after delivery no very deleterious effect on final outcome would be expected. This is not true if retarded growth has been present from mid-pregnancy or if the small-for-dates infant is delivered into an environment lacking in nutrition or psychological stimulation. Studies of long-term outcome of small-for-dates infants have shown conflicting results. Early studies were retrospective and evaluated outcome of small-for-dates babies born during the 1950's; these reported mental deficiency to be common (Warkany et al., 1961;

Barker, 1966). Drillien (1970) found the mean IQ to be lower in small-for-dates infants raised in working class homes than in similar infants born to middle class mothers.

The brain of small-for-dates babies may be damaged not only by the direct effects of intrauterine malnutrition but also by such perinatal factors as asphyxia and hypoglycaemia; their brains may be considered "primed" for further damage (Pape and Fitzhardinge, 1981). Improved perinatal care may thus diminish the incidence of brain damage, and more recent studies have generally been more optimistic about outcome although disagreement continues to exist. Thus, Babson and Kangas (1969) found no difference in IQ scores at 4 years of age between small-for-dates infants and normal birthweight controls. Vohr et al., (1978) showed that pre-term small-for-dates infants had similar developmental testing results at 2 years of age, to those in appropriately grown pre-term controls of similar birthweight. On the other hand, behavioural and motor differences have been noted in small-for-dates neonates by Michaelis et al. (1970) and by Low et al. (1978); in their preliminary findings of a prospective study of outcome in 88 small-for-dates infants the latter authors noted significant differences in developmental indices assessed at 12 months of age and compared with controls. Fitzhardinge and Steven (1972b), in their follow-up study of small-for-dates infants, found major neurological problems to be rare but minimal cerebral dysfunction, speech defects and poor school performance to be common despite normal mean IQ. Gross et al. (1978) found that small head circumference and abnormal neurological findings in small-for-dates infants in the newborn period were associated with later neurological deficit.

There is some evidence that antenatal identification of the small-for-dates fetus with subsequent optimal management may improve long-term intellectual outcome (Rhodes, 1973).

3: DETECTION OF THE SMALL-FOR-DATES FETUS:

Introduction

Clinical Assessment

Risk Assessment

Biochemical and Haematological Assessment

Miscellaneous Assessment

INTRODUCTION

As has been discussed, there are a large variety of reasons why an individual fetus may be small-for-dates; the degree and type of risk which that fetus faces also varies widely. Although assessment of the wellbeing of the growth retarded fetus will not be discussed until the next section, it may be stated now that the risks of intrauterine death and perinatal asphyxia can, to a large extent, be predicted by certain biophysical tests. However, in the absence of other pregnancy complications, the fetus must be identified antenatally as small-for-dates before these forms of assessment are implemented. This section will consider the different techniques and strategies which have been advocated to aid detection of the small-for-dates fetus; ultrasound techniques will not be described here but are discussed in detail in Chapter 2.

CLINICAL ASSESSMENT

Abdominal palpation has been the main method with which to identify the small-for-dates baby antenatally. The size of the fetus is judged and compared to that expected at the given gestational age. Repeated palpation by the same obstetrician over a period of time may indicate a failure of growth of the fetus, and clinical examination may give an impression of oligohydramnios to provide further evidence of growth retardation. However, abdominal palpation is not precise, and varying thickness of the maternal anterior abdominal wall and varying volumes of amniotic fluid may distort perception of fetal size. In addition, Loeffler (1967) reported that although prediction of birthweight by abdominal palpation was satisfactory when the fetus was of average size, its accuracy decreased at each extreme of the birthweight range. He found that about 60% of predictions of babies weighing less than 2.3 kg at birth had been inaccurate by over 450 g. and in each case the predicted birthweight had been overestimated. Most published series have reported detection rates of small-for-dates fetuses by abdominal palpation, during routine antenatal care, to range between only 30% and 50% (Campbell 1974a; Hall et al., 1980; Rosenberg at al., 1982a).

Tape measurement of abdominal girth was not found to be of any value by Elder et al. (1970) in detecting the small-for-dates fetus but there has, recently, been renewed interest in tape measurement of symphsial-fundal height. Using this, Westin (1977) described 68% detection of small-for-dates fetuses with a false-positive rate of 11% in an unselected series of 428 pregnancies, and Belizan et al. (1978) reported 86% detection with a false-positive rate of 10% in a study of 139 patients. Quaranta et al. (1981) in a retrospective study of 138 high risk patients quoted a sensitivity of 73% in detection of small-for dates fetuses with a false-positive rate of 21%. Rosenberg and colleagues (1982b), however, studying fundal height measurement in a larger series of 761 women during routine antenatal care found that only 56% of small-for-dates fetuses were detected, with a false-positive rate of 15%. Thus, while fundal height measurement is simple and inexpensive and therefore particularly suitable for use in developing countries (Belizan et al., 1978), its use in ordinary clinical practice appears to leave many small-for-dates fetuses undetected.

Thomson and Billewicz (1957) described an increased incidence of low birthweight babies born to mothers who gain little weight during pregnancy. This was investigated further by Elder et al. (1970) who, in a retrospective study, found mean weekly weight gain among mothers who produced small-for-dates infants to be 0.78 lbs per week in contrast to 0.86 lbs per week in normal controls - this difference reaches statistical significance. These authors studied prospectively 841 apparently normal pregnant women and found the incidence of small-for-dates babies was 5% when weight gain was normal, 16% when weight was static and 15% when weight dropped. Whilst 77% of small-for-dates babies were born to mothers with abnormal weight profiles, the specificity and the predictive value of the technique were low, 50% and 16% respectively. Mann et al. (1974) found no difference in weight gain between pregnancies resulting in a small-for-dates fetus (detected antenatally), those resulting in a small-for-dates fetus (not detected antenatally) and those resulting in normally grown babies. Gordon et al. (1978) found weight gain to be of no value in predicting "fetal risk" (such risk including the delivery of a small-for-dates fetus).

RISK ASSESSMENT

Additional strategies to aid detection of fetal growth retardation have evolved. The main approach is to define a group of women at high risk of producing a small-for-dates infant so that intensive antenatal monitoring may be selectively implemented to identify those fetuses that are, in fact, growth retarded and to guide subsequent management. The criteria used to identify such high risk groups are based on epidemiological factors, past reproductive performance, and the occurrence during the current pregnancy of complications known to be associated with growth retardation. There has not, however, always been unanimity as to what maternal factors are associated with fetal growth retardation (Fedrick and Adelstein, 1978). In a study of 182 women who produced small-for-dates infants Low and Galbraith (1974) found that 18% had obstetric complications such as pre-eclampsia or antepartum haemorrhage, 15% had had obstetric problems in a previous pregnancy (including a previous small-for-dates infant), 18% had what was termed pregnancy complications such as twins or postmaturity, and 8% had a significant maternal disease; 48% of these patients had no high risk features. On analysing the 1958 British Perinatal Mortality Survey data, Fedrick and Adelstein (1978) found that the risk of bearing a small-for-dates infant correlates with pre-pregnancy weight, maternal height, smoking, nulliparity, low social class, maternal employment, previous small-for-dates infant, threatened abortion and severe pre-eclampsia. From these data a scoring system was developed to predict the risk of having a small-for-dates baby (Adelstein and Fedrick, 1978). When it was applied, however, to 490 singleton pregnancies the authors found that 20% of primigravidas would have been identified as high risk but that only 8% of this group were actually delivered of small-for-dates infants, and that as many as 54% of the small-for-dates babies in the primigravid group were born to low risk mothers. Although the scoring system proved rather better in parous patients it was concluded that this approach was not effective. An evaluation of risk assessment in the Queen Mother's Hospital gave broadly similar results which are described in Chapter 3.

BIOCHEMICAL AND HAEMATOLOGICAL ASSESSMENT

Oestriol estimation has been used for many years as a means of assessing fetal growth (Macnaughton, 1967). Whilst there is general agreement that oestriol levels, in blood or urine, tend to be depressed in the presence of retarded fetal growth, overlap with results from normal pregnancies may be considerable (Tulchinsky, 1977). Thus, McFadyen et al. (1980) in a recent study found 10% of urinary oestrogen results from small-for-dates pregnancies to be above the mean for the whole population. There is a large literature on the use of oestrogen assays in obstetrics and, in keeping with the theme of this thesis, emphasis is placed on studies which have considered the role of oestrogen assay as a screening procedure to detect the small-for-dates fetus. This has been recommended by such authors as Beischer et al. (1968) who found 19 of 34 small-for-dates fetuses to be associated with low urinary oestriol results. Barnard and Logan (1972) evaluated urinary oestriol as a screening tool and found that, at 31 weeks, 70% of normally grown babies would have to be incorrectly identified as possibly growth retarded to allow detection of 95% of small-for-dates fetuses. Nielsen (1983) found 19% of small-for-dates babies to be identified by low serum oestriol levels. Duenholter et al. (1975) conducted a prospective randomised controlled trial of plasma oestriol estimation in high risk pregnancies and found no beneficial effect on fetal outcome. Wilde and Oakey (1975) have reviewed the relevant literature and concluded that oestrogen estimation is of little value in the diagnosis of retarded fetal growth. This should be distinguished from the possible value of oestrogen estimation to assess feto-placental function after the diagnosis of fetal growth retardation has been established by other means.

Human placental lactogen (HPL) is a protein produced by the syncytiotrophoblast, and levels in the mother correlate, although poorly, with placental and fetal weights (Hull and Chard, 1976). Like oestriol assay, HPL estimation has been recommended as a screening test to predict fetal distress (Letchworth and Chard, 1972; England et al., 1974; Spellacy et al., 1975). It has also been advocated as a means

of detecting the small-for-dates fetus, by Spellacy et al. (1976) who, however, reported a detection rate of only 19% by HPL values less than the generally accepted lower limit of normal (4 mg/ml) after 36 weeks. Josimovich et al. (1970) and Zlatnik et al. (1979) found, respectively, only 5 of 15 and 3 of 18 small-for-dates babies to be associated with low HPL values. The more recently discovered placental proteins (Schwangerschafts protein 1 and pregnancy associated plasma proteins A and B) have, likewise, proved disappointing as indices of retarded fetal growth (Trudinger et al.,1979; Hughes et al., 1980; Bischof and Klopper, 1983).

Dunlop et al. (1978) reported increased haematocrit, and increased haemoglobin and uric acid concentrations in a small series of small-for-dates pregnancies. Increased haemoglobin concentration was confirmed by Koller et al. (1979), this finding presumably reflecting the decreased plasma volume found in such pregnancies (Gibson, 1973) with resulting haemoconcentration. There is insufficient evidence to indicate that such tests would be suitable as screening procedures to detect small-for-dates fetuses.

Whigham et al. (1980) compared plasma uric acid estimation with total plasma oestriol, HPL, urine oestrogen/creatinine ratio and Factor VIII related antigen coagulant activity ratio in detecting the small-for-dates fetus. HPL assay proved better than the other hormonal methods assessed, and uric acid concentration was confirmed to be elevated in the small-for-dates group. However, the Factor VIII ratio, an index of endothelial stress (Whigham et al., 1979), proved most useful by predicting 17 of the 21 babies that were small-for-dates at birth.

There is a higher incidence of both pre-term and small-for-dates infants born to mothers with elevated serum alpha-fetoprotein levels during the second trimester, but this test does not provide sensitive prediction of small-for-dates infants (Brock et al., 1980).

The presence or absence of phosphatidylglycerol (PG) in amniotic fluid has been shown to be a very sensitive predictor of the risk of respiratory distress syndrome in the newborn (Whittle et al., 1982).

Gross and colleagues (1980) have recommended amniocentesis to measure PG concentration as a means of predicting small-for-dates infants. Their paper is unconvincing. Having excluded normal birthweight babies to study only those of low birthweight, they found that a concentration of PG of more than 7% would differentiate small-for-dates fetuses from normally grown pre-term babies with a sensitivity of 64% and a specificity of 74%. This probably merely reflects differing mean gestational age between these two groups which was unspecified. The widely held belief that growth retardation accelerates fetal lung maturation (Gluck and Kulovich, 1973) lacks confirmatory scientific evidence (Gunston and Davey, 1978).

MISCELLANEOUS ASSESSMENT

Verma et al. (1980) have proposed the hypothesis that fetal growth retardation and pre-eclampsia result from a spectrum of maternal vascular disorders which, if localised to the uterine vasculature manifest as growth retardation, and, if generalised, manifest as pre-eclampsia (with or without growth retardation). The so-called "roll over test" has been advocated as a means of predicting the development of pre-eclampsia (Gant et al., 1974) and has been studied as a possible means of predicting the delivery of a small-for-dates infant (Verma et al., 1980). These latter authors found that 8 of 9 small-for-dates babies were predicted by a positive roll-over test (in 4 of these pregnancies there was associated pre-eclampsia); of the remaining 29 patients with positive tests, 16 developed pre-eclampsia without fetal growth retardation and 13 were normal. This requires further study.

Russell and Lewis (1981) have recommended subjective assessment of fetal fat thickness on X-ray films as a means of detecting the small-for-dates fetus. Their assessments at less than 36 weeks, when diagnostic information is of greater value, were less accurate than those performed later in pregnancy. At this point it is relevant to discuss radiological assessment of "maturity" in small-for-dates fetuses. It is now standard teaching that the lower femoral epiphyses appear on X-rays at around 36 weeks and the upper tibial epiphyses at around 38 weeks (Hartley, 1957). There may, however, be a striking

delay in epiphyseal appearance in small-for-dates fetuses. Thus, Scott and Usher (1964) found that 37% of small-for-dates babies after 36 weeks had no radiologically detectable lower femoral epiphyses; Robinson et al. (1979) found a bone age discrepancy of 3 to 4 weeks in almost half the small-for-dates fetuses in their series.

In a small study of high risk patients MacDonald (1972) demonstrated a higher incidence of small-for-dates babies (15%) born to mothers whose cervical mucus displayed ferning after 16 weeks of pregnancy. This has not, to the author's knowledge, been investigated further.

4: OBSTETRIC MANAGEMENT OF THE SMALL-FOR-DATES FETUS

As discussed earlier in the chapter, some of the hazards of fetal growth retardation may be avoided by antenatal detection of the small-for-dates fetus, with subsequent planned delivery by induction of labour or elective Caesarean section at the optimal time. Among factors which influence such timing are the presence of other pregnancy complications such as pre-eclampsia, previous obstetric history, the severity of growth retardation as evaluated clinically or by ultrasound, assessment of amniotic fluid volume, and the ripeness of the cervix (Calder, 1979). Amniocentesis to assess fetal lung maturation is frequently of crucial importance in deciding when delivery should occur. Earlier delivery poses a greater risk of respiratory distress syndrome, failed induction of labour and prolonged separation of the baby from the mother; later delivery poses a greater risk of intrauterine death, intrapartum asphyxia and severe variable decelerations of the fetal heart rate during labour due to umbilical cord compression resulting from increasing oligohydramnios. Of great value in identifying the optimal timing of intervention are the results of assessment of fetal wellbeing. Such assessments may be biochemical, such as oestriol or HPL estimation, or biophysical, such as antepartum cardiotocography or observation of fetal breathing movements, and are discussed below. Whether intervention should take the form of induction of labour or of elective Caesarean section is based on the above factors and, like timing, needs to be individualised.

Continuous fetal heart rate monitoring during labour should be implemented in all cases as recommended by Odendall (1976) who found an increased incidence of early, late and variable decelerations among small-for-dates fetuses. Early recourse to fetal scalp blood pH estimation should be undertaken because of the increased risk of metabolic acidosis associated with fetal heart rate decelerations (Lin et al., 1980) and the threshold for Caesarean section should be lowered. The small-for-dates fetus appears to tolerate vaginal breech delivery poorly (Hutchins, 1980). A paediatrician should be present at delivery and the baby should be closely monitored after birth; early feeding should be instituted to avoid hypoglycaemia.

The final part of this chapter will consider those techniques of

assessment of fetal wellbeing which may allow the management of the small-for-dates fetus and the planning of the timing and mode of delivery to be performed in a rational and individualised fashion.

As has been discussed, biochemical assessments have proved to be inaccurate means of detecting the small-for-dates fetus. Such techniques may, however, be of value after the fetus has been diagnosed as small-for-dates by other means, by helping to differentiate between those fetuses that are at particularly high risk of perinatal death and damage, and those that are not. Few published reports consider specifically small-for-dates pregnancies but Wilde and Oakey (1975), in a review of seven reports of oestrogen excretion in such pregnancies, quote the combined perinatal mortality rate in the low oestrogen group to be 37% compared with 27% in the normal oestrogen group; these very high rates reflect, in part, the fact that most of the studies were published during the 1960's. In a recent study (McFadyen et al., 1980) urinary oestrogen excretion was low in all seven cases of intrauterine death when assay was performed within one week of fetal demise; some of the fetuses were small-for-dates. Assay of HPL, however, was not found to effectively predict outcome of small-for-dates fetuses by Josimovich et al. (1970) and Zlatnik et al. (1979).

Detection, by amniocentesis or amnioscopy, of meconium staining of the amniotic fluid is of questionable value in predicting fetal outcome (Miller, 1979) and this technique has been generally superceded by alternative means of antepartum assessment.

In conditions of chronic fetal hypoxia, such as may be found in intrauterine growth retardation, fetal movement may decrease and then cease some 24 to 48 hours before intrauterine death (Sadovsky et al., 1974). Normal fetal movement, as monitored by "kick counts", is generally associated with good outcome (Pearson and Weaver, 1976) and this also applies to small-for-dates fetuses (Jarvis and MacDonald, 1979). Whilst kick counts are of undoubted value, more sophisticated evaluation is usually necessary when the fetus is small-for-dates and especially when fetal movement decreases.

Boddy and Dawes (1975) described an absence of normal fetal breathing movements with the appearance of "gasping" some 24 to 72 hours before the intrauterine death of 10 fetuses, "some of which" were small-for-dates. The continued presence of normal fetal breathing movements, in contrast, indicated good prognosis. Other workers have also studied ultrasound assessment of fetal breathing movements as an index of fetal wellbeing and some have found it useful (e.g. Trudinger et al., 1979) whilst others have found prolonged fetal apnoea to be not uncommon in association with good outcome (Fox and Hohler, 1977). A practical difficulty found with this technique is the large number of extraneous factors which may influence fetal breathing, including abdominal palpation and maternal smoking, eating and drug administration. Other aspects of dynamic fetal function have also been studied. It is possible, for example, to calculate the rate of fetal urine production by repeated ultrasound measurement of fetal bladder volume (Campbell et al., 1973). The rate of urine production may be greatly decreased in small-for-dates fetuses, thus accounting for the frequently associated oligohydramnios, but this does not predict the development of asphyxia during labour (Wladimiroff and Campbell, 1974).

The oxytocin challenge test (OCT), which involves antepartum continuous fetal heart rate recording while uterine contractions are (usually) induced by oxytocin infusion, has been shown to be a useful test of fetal wellbeing - a negative test (i.e. absence of repetitive late decelerations) being a reliable indication of fetal health (Freeman, 1975). This technique has been evaluated by Cetrulo and Freeman (1977) in the management of 99 babies confirmed to be small-for-dates at birth. The perinatal mortality rate was 18% in the 27 pregnancies with a positive OCT, and 1% in the remaining cases in which the test was negative. Seven of the 11 perinatal deaths occurred antepartum and three of these were predicted by a positive OCT. Because of technical problems in some of the tests, however, the authors judged that there was only a single genuine false-negative test. Schulman et al. (1977) found in a study of OCT in high risk pregnancies that 33% of fetuses with positive tests were small-for-dates at birth. Although the OCT is useful in evaluating fetal condition and utero-placental reserve,

it is time-consuming, possibly occasionally dangerous and not easily repeatable and, in consequence, non-stress antepartum cardiotocography has been increatingly employed in the assessment of high risk pregnancies (Flynn and Kelly, 1977). This was evaluated by Flynn et al. (1979) in 57 pregnancies which terminated in the delivery of a small-for-dates infant (birthweight less than the 10th percentile). Surprisingly only four of these fetuses had normal reactive traces but this indicated a good prognosis; of 16 fetuses showing ominous traces with repetitive late decelerations, six died before labour and five of the remaining 11 had low Apgar scores. The consensus of opinion is that normal antepartum cardiotocography indicates good prognosis and can allow conservative management until a suitable time for delivery. Abnormal traces indicate poorer prognosis depending on the severity of the abnormality, but the finding of an abnormal trace does not necessarily predict poor fetal outcome (McCune et al., 1983). It is the opinion of the author that antepartum non-stress cardiotocography is the test of fetal wellbeing most useful in the management of the small-for-dates fetus.

CHAPTER 2.

DIAGNOSTIC ULTRASOUND

HISTORY

PHYSICAL AND TECHNICAL ASPECTS OF ULTRASOUND

SAFETY

ULTRASOUND ASSESSMENT OF GESTATIONAL AGE

ULTRASOUND ASSESSMENT OF FETAL GROWTH

HISTORY

The history of the development of ultrasound as a diagnostic tool has been charted by Kratochwil (1978). As a direct result of the sinking of the transatlantic passenger liner, Titanic, the first practical application of ultrasound was to determine the position of icebergs; further advances in the application of ultrasound to marine technology occurred during the First World War with the need to detect German submarines blockading the United Kingdom. Following that war, the technique was used in industry to detect flaws in metal structure.

The first exercise to use ultrasound as a diagnostic technique in medicine was by the Austrian neurologist Dussik in 1938. His attempts to outline the adult brain and its ventricles failed because of the high acoustic impedance of skull bone. Further refinements were made in ultrasound instrumentation during the Second World War for military purposes and, using war-surplus equipment, Howry in 1947 in Denver started to investigate the potential of ultrasound in medical diagnosis. Later, with Holmes, he produced high quality images of upper abdominal organs but his system had the important disadvantage that it necessitated the immersion of the patient in a bath of water. In 1954, Professor Ian Donald in Glasgow started his research from which ultrasound was to emerge as a practical and useful diagnostic technique. Donald has recently recounted the, often amusing, story of the first steps in this process (Donald, 1980). Together with an engineer T.G. Brown, he constructed the first contact ultrasound scanner which, because the ultrasound transducer was brought into direct contact with the patient's skin, made diagnostic ultrasound a practical proposition. In a series

of publications Donald and colleagues described the usefulness of ultrasound in the differential diagnosis of abdominal masses (Donald et al., 1958; Donald, 1963), the diagnosis of hydatidiform mole (Donald and Brown, 1961) and the detection of blighted ova, twin pregnancies and placenta praevia (Donald and Abdulla, 1967). From these beginnings diagnostic ultrasound became established in obstetric practice, and most sophisticated maternity units throughout the world now possess ultrasound equipment. Of the many uses to which ultrasound has now been applied in obstetrics those of relevance to this thesis, namely assessment of gestational age and of fetal growth and size, will be discussed in detail later in this chapter.

PHYSICAL AND TECHNICAL ASPECTS OF ULTRASOUND

Ultrasound may be defined as mechanical vibration occurring at frequencies above the range of human audibility, i.e. above about 16 kHz. In diagnostic work frequencies of several million cycles per second are used (MHz). Within this range, ultrasound exhibits certain special properties; of diagnostic importance is the possibility of producing focussed or highly directional beams. The original static ultrasound scanners utilised a single disc-shaped slice of piezo-electric ceramic to convert electrical energy to ultrasound energy and vice versa. The piezo-electric effect had been discovered by the Curie brothers during the nineteenth century but their findings were ignored for decades (Kratochwil, 1978). The two flat surfaces of the piezo-electric crystal disc are coated in metal to form conducting electrodes. When a voltage is applied across the elctrodes in one direction, the disc becomes thicker with a smaller radius; a voltage applied in the opposite

direction causes the disc to become thinner with a greater radius. Application of an alternating voltage thus results in a forwards and backwards movement of the transducer face to propogate waves of sonic energy. Each time the face moves forward a new crest is formed; the distance that separates the crests is the wavelength.

The physical aspects of diagnostic ultrasound have been comprehensively reviewed by Talbert and Campbell (1972). Different tissues provide different degrees of impedance to the passage of ultrasound and this enables reflection to occur at tissue interfaces. The process of reflection is crucial in providing diagnostic information with ultrasound, and the reception and processing of reflected echoes will be discussed shortly. The ideal ultrasound beam would be needle thin to give the finest detail, but this is not possible because ultrasound shares with other forms of wave energy the property of diffraction. Higher frequencies produce more precise beam formation, and focussing is an alternative means of overcoming the effects of diffraction, at least around the focal point of the beam. Refraction, another property of wave motion, is of minimal importance in obstetric ultrasound where thick bone layers do not lie in the beam path.

Essentially, ultrasound systems are used to determine the position of a structure. A short burst of ultrasound, lasting a few cycles, is repetitively transmitted into the tissue to be investigated (pulsed ultrasound). After each pulse the electronic circuitry supplying the transducer is effectively disconnected and the receptor electronics activated. When an interface of tissues of different acoustic impedance is situated in the path of the beam, some of the ultrasound is reflected.

The piezo-electric crystal of the transducer has the additional and converse property of generating a voltage across the terminals when it is mechanically stimulated by reflected ultrasound energy. This is detected by the receptor electronic system. Combining the information received - that an echo occurred, that the transducer was positioned at a certain angle, and that the echo was received a certain measured time after transmission - the ultrasound system can determine the position of a structure. By transmitting the ultrasound beam into a complex biological medium, such as the uterus and fetus, a series of echoes are reflected from the different tissue interfaces. This information may be displayed in different ways. The simplest display is the A-mode, so-called from its use in radar (Talbert and Campbell, 1972). The A-mode provides a simple linear display, with received echoes appearing as peaks, and it was formerly used almost universally as the optimal means of fetal measurement. Artificial echoes ("electronic calipers") were employed in most systems to be superimposed on the A-mode display to calculate distance, based on the time delay between reception of echoes and the assumed sound velocity in the tissue investigated. Information may also be displayed in the time-position (TP) mode which is a graphical display depicting, in effect, the A-mode display over a period of time. This is convenient for demonstrating rapid tissue movement and has been widely used in echocardiography but has little practical application in obstetric work. The B-mode display builds up a two-dimensional image of the tissues underlying the sweep of the transducer, as moved by the operator. This necessitates the equipment "knowing" where the transducer is positioned and at what angle it is directed at all times. This can

provide a high quality image as long as significant tissue movement does not occur while the display is being constructed.

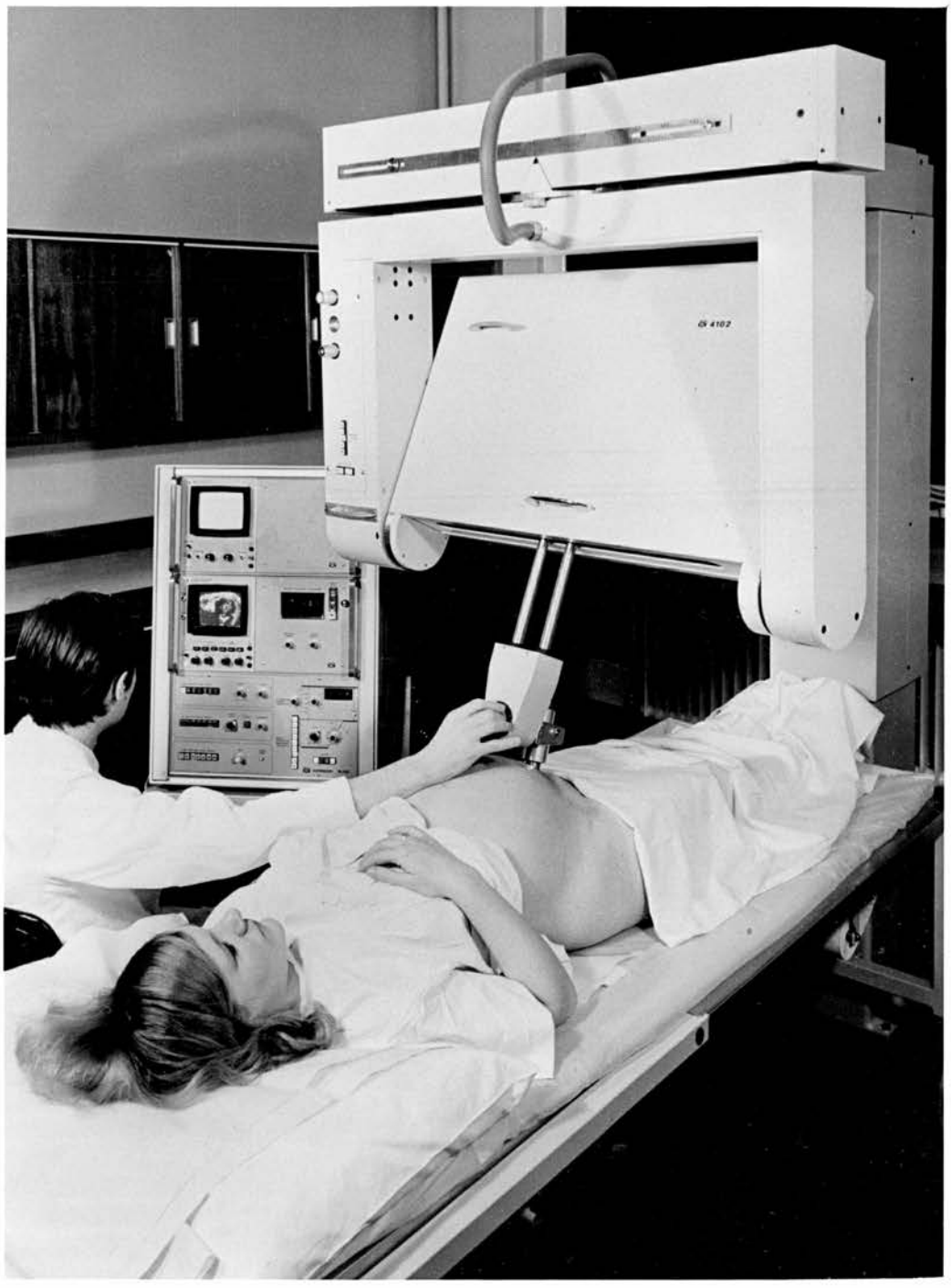
The above remarks relate mainly to the single transducer static B scanners which were, for several years, the only commercially available diagnostic ultrasound systems. More recently alternative forms of ultrasound equipment have become available (Hall, 1980). The most successful have been the real-time linear-array scanners (Campbell and Little, 1978). These equipments produce a two dimensional "moving" image from a long hand-held transducer. The linear-array transducer is comprised of many elements, different groups of which are energised in sequence. Compared with the static B scanner, real-time scanners are less expensive, simpler to operate and are particularly useful for study of what is often a continuously moving structure, namely the fetus. In most aspects of obstetric ultrasound the real-time scanner is at least as useful as the static B scanner; in the opinion of the author, exceptions are precise fetal measurement and possibly placentography. Alternative types of ultrasound equipment include mechanical real-time scanners (which have a small scanning head with internal rotating transducers designed to provide a sector scan), phased-array scanners (which also provide a sector scan but by using variable electronic delays rather than mechanical rotation), water bath scanners (more sophisticated versions of the original Howry model which produce very high quality images via an immersed transducer rather than of an immersed patient) and Doppler scanners (which are suitable for the study of flow dynamics in blood vessels).

The ultrasound equipment employed in the studies reported later in

this thesis were of the linear-array real-time or static B scan types. The former equipment (mainly Diagnostic Sonar Systems 85 and 185, Livingstone, Scotland) were used for assessment of gestational age in early pregnancy. The latter equipment (Diasonograph 4102, Nuclear Enterprises/now Fischer Ultrasound, Edinburgh, Scotland) was used for ultrasound measurement during the third trimester (Figure 2 - 1). In addition to standard measuring facilities on the Diasonograph, an electronic area and circumference measuring system (Figure 2 - 2) was used for certain fetal measurements during third trimester ultrasound study. This system was constructed by J.E.E. Fleming and A.J. Hall in the obstetric ultrasound laboratory at the Queen Mother's Hospital, Glasgow. Similar systems have become available commercially since these studies were commenced. This system has been described in detail elsewhere (Fleming et al, 1978) but will be described briefly here:

> Modern diagnostic ultrasound equipment utilises analogue or digital scan converters which provide grey-scaled images and thus improved picture quality when contrasted to the old direct-view storage tube displays (Hall, 1980). However, for technical reasons, the television monitors which are necessary to display the grey-scaled images introduce spatial distortions and uncertain scale factors which mean that accurate measurements cannot be obtained directly from these displays (Fleming et al., 1978). The Fleming and Hall system uses the standard electronic calipers of the Diasonograph to permit measurement at an earlier stage in image processing. As far as the operator is concerned, however, measurement appears to take place on the high quality grey-scaled image; one caliper dot is positioned in the centre of the image to be measured, the other is steered around the periphery using the remote joystick (Figure 2 - 2). The radius is measured at constant angular increments and area and circumference measurements thus automatically calculated. In a water bath experiment to study accuracy of measurement, mean errors of only 1.8% (circumference) and 2.5% (area) were obtained; corresponding figures using a map measurer for circumference and a planimeter for area were 3.3% and 5.5% respectively (Fleming et al., 1978). The measuring system is not only more accurate but it is easier and quicker to use than alternative techniques.

Figure 2 - 1



Diasonograph 4102, Nuclear Enterprises, Edinburgh.

Figure 2 - 2

The electronic area and perimeter measuring device.
The joystick is on the right.

SAFETY

Following the findings of Stewart and colleagues (1956; 1958) that the incidence of childhood malignancy is increased after prenatal exposure to X-rays, much attention has been paid to the subject of whether ultrasound examinations may be harmful to the developing fetus. This has been comprehensively reviewed by Hill (1968), Taylor and Dyson (1972), Donald (1976), Febrikant (1977), Abdulla (1978) and Baker and Dalrymple (1978).

Ultrasound may have the following three effects in biological tissue : cavitation, thermal effects, and "direct" effects as proposed by Hill (1978). Cavitation is more likely to occur with constant insonation, and it is probably completely absent when ultrasound is transmitted in pulses as in diagnostic work (Hill, 1968; Donald, 1976). Thermal effects are also insignificant since a rise in temperature can be induced only by energy levels far in excess of those used diagnostically. The "direct" effects represent as yet uncertain mechanisms of action on tissue and if harm does result from insonation it is probably by these mechanisms. Many in vitro experiments have been performed to assess the safety of ultrasound (see Abdulla, 1978). The only report to describe evidence of damage was that of Macintosh and Davey (1970) which appeared to demonstrate ultrasound - induced chromosomal damage. After much controversy the principal author was unable to replicate these findings and attributed his original results to experimental artifact (Macintosh et al., 1975). Animal studies have failed to indicate any harmful effect at energy levels used for diagnostic work. A study of fetal outcome after ultrasound examination, carried out in New York, Glasgow and Lund, showed no adverse features in the insonated group (Hellman et al., 1970). Deafness is not more common after in utero exposure to ultrasound (Donald, 1976).

The consensus of opinion is that diagnostic ultrasound has a wide margin of safety and there has been no evidence of harm demonstrated after exposure to ultrasound at diagnostic energy levels.

ULTRASOUND ASSESSMENT OF GESTATIONAL AGE

Accurate knowledge of gestational age is important in modern obstetric practice to allow detection of the small-for-dates fetus by clinical or other means and to indicate the optimal timing of induction of labour or elective Caesarean section, when indicated. In addition, the normal values of some tests of fetal wellbeing and of others used to help detection of fetal anomalies (e.g. maternal serum alpha-feto-protein) change as pregnancy advances; a knowledge of gestational age is necessary for proper interpretation. Usually gestational age is calculated from the date of the start of the woman's last menstrual period. However, this calculation was found to be unreliable, for a variety of reasons, in 40% of patients attending the Queen Mother's Hospital (Robinson, 1978). Ultrasound measurement of the fetus in early pregnancy has been shown to be more accurate in the estimation of gestational age than alternative means of assessment including clinical examination (even in the first trimester) (Beazley and Underhill, 1970), the date of quickening (Grennert et al., 1978) or radiological evaluation in late pregnancy (Robinson et al., 1979).

In early pregnancy fetal growth is rapid, there is little biological variation in fetal size, and pathological growth retardation is uncommon. For these reasons measurement of fetal size by ultrasound provides accurate estimation of gestational age. During the first trimester fetal crown-rump length is measured using the technique of Robinson (1973); this is accurate to within ± 5 days in 95% of cases (Robinson and Fleming, 1975) and has proved more accurate than gestation sac volume measurements (Robinson, 1975). The original work on crown-rump length measurement was performed using static B scanners, but Adam et al. (1979) have shown that accurate measurements may be obtained using real-time systems.

The standard ultrasound method of assessing gestational age during the second trimester is by measurement of the fetal biparietal diameter (BPD). Most of the important original work on this was performed by Campbell, initially in Glasgow and subsequently in London. Using his combined A and B mode technique (Campbell, 1968) on static B scanners,

BPD measurements are highly accurate, (Campbell, 1970) and reproducible (Campbell, 1973). More recent reports have also shown BPD measurements using real-time scanners to be accurate (Docker and Settatree, 1977; Adam et al., 1978; Osinusi et al., 1980). BPD growth averages 2.8 mm per week between 20 and 30 weeks, and 1.5 mm per week after 30 weeks (Campbell, 1969). This together with the progressively greater biological scatter of BPD values as pregnancy advances, reinforces the point that ultrasound measurement to assess gestational age is maximally accurate when performed as early as possible in pregnancy. BPD measurement before 30 weeks will predict the date of delivery to within $\pm$ 2 weeks in 80% of patients with "unknown dates" (Underhill et al., 1971).

Recently ultrasound measurement of femoral length during the second trimester has been proposed as an alternative or additional means of assessing gestational age (O'Brien et al., 1981).

ULTRASOUND ASSESSMENT OF FETAL GROWTH

The BPD may also be measured serially during the third trimester to assess fetal growth. Using only a simple A-mode system, Willocks and colleagues showed that serial biparietal cephalometry could identify the small-for-dates fetus (Willocks et al., 1965; 1967; Willocks, 1971). Subsequently Campbell, using his combined A and B mode technique, constructed BPD charts based on the measurement of normal fetuses from 13 weeks of pregnancy (Campbell and Newman, 1971) and showed that up to 73% of small-for-dates fetuses could be detected antenatally by serial measurement of the BPD (Campbell and Dewhurst, 1971). Different patterns of abnormal BPD growth may be delineated, including 'late flattening' (abrupt cessation of growth, usually in late pregnancy), 'low growth profile' (subnormal growth rate from early pregnancy - the pattern seen in growth retardation associated with fetal anomaly; Campbell, 1974b) and 'catch-up-growth' (transient cessation of growth with subsequent acceleration; Bamford et al., 1977). Serial biparietal cephalometry has been compared with urinary oestrogen assay (Campbell and Kurjak, 1972; Robinson et al., 1973) and found to be superior in the detection of small-for-dates fetuses although a combination of both techniques proved more efficacious than either alone.

Several problems are, however, encountered in the use of serial biparietal cephalometry. For accurate measurement of the BPD, the correct angulation of the ultrasound transducer is crucially important (Watmough et al., 1974; Blackwell, 1978). This is often difficult and may be impossible when the fetal head is in a direct occipito-anterior or occipito-posterior position or when it is low in the maternal pelvis; the accuracy of BPD measurement is highly dependant on the skill and experience of the operator (Davison et al., 1973a; 1973b; Campbell, 1973). Further, to be of value BPD measurement must be performed on repeated occasions thus delaying the diagnosis that the fetus appears growth retarded and, for logistic reasons, restricting the number of patients in whom this procedure may be performed. Robinson (personal communication) analysed retrospectively the results of serial biparietal cephalometry, performed on 331 high risk patients at the Queen Mother's Hospital, to evaluate this technique in actual practice. He found that no less than 93 of the BPD curves (28%) were difficult or impossible to interpret for a variety of reasons; only 25 of the 39 babies which were small-for-dates at birth (64%) had had demonstrably abnormal BPD growth curves; and of the 71 fetuses with abnormal BPD curves only 25 (35%) were small-for-dates at birth. Thus, in ordinary practice in a reputable obstetric ultrasound unit, serial biparietal cephalometry is associated with high false-negative (36%) and false-positive (23%) rates. One of the reasons for the high false-negative rate (failure to detect the small-for-dates fetus) is the so-called 'brain sparing' effect (see below).

If organ weights of small-for-dates infants are compared with those of normally grown controls of similar gestational age or of similar birthweight (i.e. pre-term infants), marked differences are seen (Gruenwald, 1974). Those organs most reduced in size by intrauterine growth retardation are the spleen, liver and thymus; the brain, in contrast, is preferentially protected from the effects of growth retardation. Thus in Gruenwald's comparison of the organ weights of small-for-dates and pre-term infants, the mean liver weight of the small-for-dates group was less than that of the controls while brain weight was 40% greater. Similar findings can be demonstrated by animal

experiments in which fetal growth retardation is induced by ligation of vessels supplying the placental bed (Winick, 1971), and among infants dying of alimentary malnutrition during the first months of life (Naeye, 1965c). It should be stressed that this phenomenon of brain sparing refers to the physical size of the organ and implies little about the possible effects of intrauterine growth retardation on the functional capacity of the developing brain (Hull et al., 1978). Also worthy of note is the fact that, despite the brain sparing effect, the brains of small-for-dates infants are of less mean weight than those of normally grown babies of similar gestational age (Gruenwald, 1974); the effect is relative. Nonetheless, these findings are of importance to the detection of the small-for-dates fetus by ultrasound measurement. Serial biparietal cephalometry involves measurement of an index of the size of the fetal organ (the brain) that is least affected by growth retardation. This is illogical and accounts in part for the false-negative rates obtained with serial biparietal cephalometry.

Recently, therefore, ultrasound measurement of alternative fetal parameters has been investigated; this work has been reviewed by Deter et al. (1981; 1982). As early as 1965, measurement of the fetal thorax was described as a means of assessing fetal size (Thompson et al, 1965), although more recently attention has focused on measurements of the fetal abdomen (or trunk) at the level of the fetal liver because of the particular impact of intrauterine growth retardation on this organ. The umbilical vein has generally been taken as the marker for identification of the standard transverse fetal section (Campbell and Wilkin, 1975; Hansmann, 1977) and this practice has been followed in the studies on which this thesis is based. It has been suggested that, because the confluence of the umbilical vein with the portal sinus lies in the true transverse axis of the fetus, this should be used as the best landmark (Morin and Winsberg, 1978).

Garrett and Robinson (1971) described serial measurement of the fetal trunk (in a section between the heart and kidney) as an adjunct to measurement of the fetal head in attempting to detect the small-for-dates fetus; they did not report whether improved detection was obtained with trunk or with head measurements. Campbell and Wilkin (1975) described

measurement of trunk circumference as a means of predicting birthweight. Using a computerised extrapolation of available data they came to the conclusion that the optimal gestational age at which to screen for the small-for-dates by a single trunk circumference measurement would be 32 weeks, when it was predicted that there would be a false-negative rate of 13% and a false-positive rate of 1%. This exercise, however, seemed to be based on the assumption that small-for-dates and other fetuses remain in the same percentile size band throughout pregnancy; that this does not always happen can be demonstrated by serial biparietal cephalometry. Subsequent work by King's College Hospital team have shown quite different results on prospective study (Little and Campbell, 1982). Many other workers have reported a prediction of birthweight by various ultrasound measurements performed shortly before delivery (Thompson and Makowski, 1970; Iannirubertо and Gibbons, 1971; Higginbottom et al., 1975; Kurjak and Breyer, 1976; Lunt and Chard, 1976; Picker and Saunders, 1976; Campogrande et al., 1977; Warsof et al., 1977; Kearney et al., 1978; McCallum and Brinkley, 1979; Poll and Kasby, 1979; Sampson et al., 1982). These studies are not directly relevant to this thesis and will not be discussed except to conclude that, generally, trunk measurements have been found to be better predictors of birthweight than have head measurements although some studies have found a combination of both to be best (Lunt and Chard, 1976; Sampson et al., 1982). Two studies have indicated that fetal length should also be measured (Picker and Saunders, 1976; McCallum and Brinkley, 1979).

In an attempt to distinguish between different types of growth retardation (rather than to detect the small-for-dates fetus) Campbell and Thoms (1977) reported on calculation of the ratio of head circumference to trunk circumference. As discussed earlier, the small-for-dates group is heterogeneous, the type and severity of risks faced by individual small-for-dates fetuses varying greatly. Identification of the particular type of growth retardation in an individual case may be of prognostic value and useful in clinical management. In growth retardation resulting from utero-placental insufficiency the neonotes characteristically have a wasted malnourished appearance with heads large in comparison to

trunks (asymmetrical growth retardation). Typically these fetuses have late flattening BPD growth curves (Garrett and Robinson, 1971; Campbell, 1974b) and a high incidence of perinatal asphyxia and neonatal hypoglycaemia (Campbell, 1974b) as one would expect as a consequence of utero-placental insufficiency. The other group of small-for-dates babies do not appear wasted at birth and are symmetrically growth retarded with overall small dimensions. Characteristically, their serial BPD curves show a low growth profile pattern (Campbell, 1974b). In contrast to the late flattening group, Campbell attributes the small size of these infants to low growth potential despite an intrauterine environment satisfactory to maintain normal growth. Thus, fetuses which are abnormal (especially chromosomally abnormal) or have suffered a major insult during the critical period of organogenesis (e.g. by rubella infection) or are small because of their genetic endowment, would be expected to fall into this group. (Campbell, 1974b) found that, if abnormal fetuses were excluded from consideration, the low growth profile group had a lower incidence of perinatal problems than the late flattening group although he did not quantify the relative risks in each group.

In a further attempt to distinguish between these two groups of small-for-dates fetuses, Campbell and Thoms (1977) used the ratio of head to trunk circumferences. The ratio was determined in 31 small-for-dates fetuses within one week of delivery; 22 (71%) had ratios above the 95th percentile (asymmetrical growth retardation) and the rest had normal values (symmetrical growth retardation). While there was a higher incidence of intrapartum fetal distress and of operative delivery in the asymmetrical group, the perinatal mortality and incidence of low Apgar Scores were similar and high in both groups. Two babies had congenital defects (cystic fibrosis and rubella embryopathy) and both were symmetrically growth retarded.

Studies of postnatal growth in small-for-dates infants are of relevance to attempts to correlate abnormal intrauterine growth patterns with their pathogenesis. Fancourt et al. (1976) showed that those small-for-dates babies that had been shown to manifest slow BPD growth before 34 weeks of pregnancy had, as a group, smaller head circumferences, heights and

weights at between 28 and 34 months of age than did the small-for-dates groups which either did not demonstrate slowing of BPD growth until after 34 weeks or did not show abnormal BPD growth. Davies et al.(1979) in a different study classified their small-for-dates infants into asymmetrically and symmetrically growth retarded groups according to the Ponderal Index (Miller and Hassanein, 1971). They found that, with the exception of weight gain in the symmetrical group during the first month, weight gain and length and head circumference growth was consistently greater during the first three months of life in both small-for-dates groups compared with infants of normal birthweight. Since both asymmetric and symmetric groups demonstrated catch-up growth following delivery it would appear that environmental growth restraint was operating in both groups. It may well be that, on the question of asymmetry and symmetry, the time of the impact of the growth retarding factor is of greater importance than the actual nature of the insult. Further study of this matter is clearly required, but in the light of available knowledge all small-for-dates fetuses should be regarded as high risk and managed accordingly.

Whilst Campbell and Thoms (1977) used head-trunk ratios to investigate the type of growth retardation, other workers have used similar measurements to detect the small-for-dates fetus. Overall, there have been few published reports on the use of trunk measurements to detect the small-for-dates fetus and these will be discussed in some detail.

Wladimiroff and colleagues (1978) studied the ultrasound measurement of 303 normal and 84 small-for-dates fetuses (defined as having a birthweight less than the 10th percentile). The BPD was measured and head area calculated by squaring the BPD value (at best an approximation of head area); chest area was measured, using a planimeter, immediately below fetal cardiac pulsation on a transverse section that included part of the fetal liver (Wladimiroff et al., 1977). Judging from the data in their 1978 paper most of the measurements in the small-for-dates fetuses were carried out after 36 weeks. Of the 84 small-for-dates fetuses 36 (42%) had small BPD measurements and 63 (75%) had small chest area measurements, indicating better detection by the latter parameter;

false-positive results were not reported. A minority of small-for-dates fetuses (36%) had abnormal head-chest area ratios.

Varma and colleagues (1979) carried out various measurements on 186 high risk fetuses at both 33 weeks and within 10 days of delivery; 35 of these were small-for-dates at birth (birthweight less than 10th percentile). Rates for the detection of small-for-dates fetuses at 33 weeks were 57% (head area), 71% (thoracic area), 80% (trunk area - measured at umbilical vein), and 83% (head-trunk area ratio) with false-positive rates ranging from 8 to 11%. Corresponding figures for measurements performed within 10 days of delivery were 74% (head area), 83% (thoracic area), 83% (trunk area) and 86% (head-trunk area ratio) with similar false-positive rates. The results found with head-trunk area ratios in this study are substantially different from those obtained by head-chest area ratios by Wladimiroff et al. (1978).

Crane and Kopta (1979) reported 100% detection of small-for-dates fetuses by head-trunk circumference ratios, with a nil false-positive rate. Their study included only 47 pregnancies, in all of which there was pre-existing evidence of fetal growth retardation; only 10 babies were small-for-dates at birth but the criteria used to define small-for-dates were not specified.

Another reported study is that of Kurjak et al. (1980). The nature of their selection of the 260 small-for-dates fetuses studied is puzzling as they were apparently selected as the only small-for-dates infants born from 40,000 pregnancies screened by ultrasound in Zagreb over a five year period. Small-for-dates was defined as birthweight less than the 10th percentile and much larger numbers would therefore be anticipated. Measurements performed included a single BPD measurement, serial biparietal cephalometry, trunk circumference (TC) and head-trunk circumference ratio (HTCR). Not all of these measurements were performed in all cases; thus, 188 patients underwent serial cephalometry and only 62 TC measurements were made. The gestational age when these measurements were performed was not specified. Detection rates of small-for-dates fetuses were reported as follows: 49% (single BPD), 52% (serial cephalometry), 84% (TC) and 80% (HTCR): false-positive rates were not mentioned.

At the Queen Mother's Hospital, Wittmann et al. (1979) investigated the measurement of nine different fetal parameters as possible screening techniques for the small-for-dates fetus using a single ultrasound examination. To assess the best method and timing of measurement, ultrasound examination was performed on 255 women at approximately 32, 34 and 36 weeks. Definition of small-for-dates was birthweight less than the 10th percentile according to the chart of Lubchenco et al. (1963), which approximately corresponds to the local Glasgow 5th percentile, and 16 infants were classified as small-for-dates at birth. Detection rates of these small-for-dates fetuses were : 44% (BPD), 71% (trunk area - TA) and 40% (crown-rump length - CRL). Similar results were obtained with the other single measurements (occipitofrontal diameter, head area, head circumference, transverse trunk diameter, antero-posterior trunk diameter and trunk circumference). Combination of measurements proved more effective, the best combination being the product of crown-rump length and trunk area (CRL X TA) which had an overall false-negative rate of 33% and a false-positive rate of 6%. However, after 235 days (33 weeks 4 days) the results were excellent, only two of 17 measurements from small-for-dates fetuses being above the demarcation line giving a false-negative rate of only 12%. Of the different head to trunk ratios assessed, the ratio of the areas proved most effective although it detected only 50% of the small-for-dates fetuses; there was an even distribution of false-negative results throughout the study period.

Duff and Evans (1981) also studied single ultrasound examinations during the third trimester. BPD, TA and TC (the latter parameters measured at the level of the umbilical vein) were measured at around 34 weeks in 140 patients, 16 of whom produced small-for-dates infants (birthweight less than the 10th percentile). Using the product of BPD and TC (or TA), 75% (or 69%) of small-for-dates fetuses were detected with a false-positive rate of 16%.

Eik-Nes et al. (1983) studied the timing of single ultrasound measurement to detect the small-for-dates fetus. 606 unselected patients were studied; all had undergone BPD measurement to assess gestational age at

17 weeks. At approximately 33 and 38 weeks further ultrasound examination was performed to measure the BPD and the 'trunk diameter' (the mean of antero-posterior and transverse trunk diameters measured at the umbilical vein). Small-for-dates was defined as birthweight 20% or more below the mean (approximately the 6th percentile) and there were 26 such small-for-dates babies at birth. Using a nomogram constructed from a previous study (Eik-Nes et al., 1982) which was designed to predict birthweight deviation from the mean, the following results were obtained : at 33 weeks the false-negative rate was 23% and the false-positive rate 22%; at 38 weeks the false-negative rate was 17% and the false-positive rate 22%.

Another ultrasound technique which has been used to detect the small-for-dates fetus, especially in the United States, is measurement of total intrauterine volume (TIUV), introduced by Hobbins in Yale. The rationale for this procedure is based on the fact that not only are small-for-dates fetuses small in themselves, but the placenta also tends to be small and the volume of amniotic fluid tends to be reduced thus resulting in overall reduced intrauterine volume. TIUV is calculated from three measured linear dimensions of the uterus. In the initial study of 96 high risk patients, 25 produced small-for-dates infants (birthweight less than the 10th percentile); 21 of these small-for-dates fetuses (75%) had abnormal TIUV measurements (Gohari et al., 1977). Surprisingly none of the normally grown babies had TIUV results below the demarcation line (minus 1.5 standard deviations from the mean as derived from measurement in normal pregnancies) but this may reflect the small numbers involved. Levine et al. (1979) studied prospectively 9 small-for-dates fetuses (birthweight less than the 5th percentile) and found abnormal TIUV measurements in all cases. These authors did not, apparently, study normal patients prospectively to evaluate the false-positive rate. Middleton et al (1982) have been unable to replicate the results of Gohari and colleagues and have found large inter-operator variability in TIUV measurement (13%). Middleton's study was retrospective and included 99 patients suspected of having a small-for-dates fetus; 20 measurements were obtained from babies which were small-for-dates at birth (birthweight less than 10th percentile). Analysis showed

that only 9 of the TIUV measurements (45%) obtained from these small-for-dates pregnancies had been abnormal. Whilst several of these measurements were obtained during the second trimester, the distribution of false-negative results appeared fairly even throughout the second half of pregnancy.

In the opinion of the author measurement of TIUV replicates many of the problems associated with abdominal palpation. Amniotic fluid may or may not be reduced in volume in small-for-dates pregnancies, and in cases of growth retardation associated with fetal anomaly there may exist polyhydramnios. The ultimate object of interest is the fetus and ultrasound measurement should be concentrated on it.

From review of all the above reports the following general points may be made :

1. There is a shortage of good studies designed to investigate the effectiveness of ultrasound-measured fetal parameters, other than the BPD, in the detection of the small-for-dates fetus.

2. Available information indicates that trunk measurements are more effective than head measurements, as would be expected from knowledge of the brain sparing effect.

3. Little is known about the value of <u>serial</u> measurement of trunk dimensions.

4. There are enormously different reported results of the percentage of small-for-dates fetuses with abnormal head-trunk ratio measurements. At present it would seem that these measurements are better employed to investigate the type of growth retardation in an individual case than to detect the small-for-dates fetus, although the significance of symmetrical and asymmetrical growth retardation is still far from clear.

5. Whether diagnostic ultrasound provides a practical and effective means of screening for the small-for-dates fetus by a single ultrasound examination during the third trimester requires further study.

CHAPTER 3.

DEVELOPMENT OF A MEANS FOR SCREENING FOR THE SMALL-FOR-DATES FETUS USING A TWO-STAGE ULTRASOUND EXAMINATION SCHEDULE

INTRODUCTION

As discussed in Chapter 1, there are a variety of reasons why an individual fetus may be small-for-dates at birth and the associated risks will vary according to the aetiology. The small-for-dates group as a whole, however, have a higher perinatal mortality rate than babies of normal birthweight (Gruenwald, 1964; Lugo and Cassady, 1971; Usher, 1971; Alberman, 1974; Naftolin and Usher, 1978; McIlwaine, et al., 1979a; Dobson, et al., 1981). While the majority of these deaths are stillbirths (McIlwaine, et al., 1979a), the neonatal mortality rate is also increased (Lubchenco, et al., 1972). The additional hazard of perinatal asphyxia (Low, et al., 1972; Perry, et al., 1976; Oh, 1977) may, like intrauterine death, be avoidable by planned delivery at an optimal time and under optimal circumstances. There therefore appears a vital need for an effective method for screening for small-for-dates fetuses early enough to permit intensive biochemical and biophysical monitoring of the state of fetal wellbeing on which to base further management, a policy which may be expected to result in improved perinatal mortality and morbidity and long term outcome.

The simple clinical techniques of abdominal palpation (Campbell, 1974; Hall et al, 1980; Rosenberg, et al., 1982a) and tape measurement of fundal height (Rosenberg, et al., 1982b) are not effective in detecting the small-for-dates fetus. It has been suggested that the clinical detection rate may be improved by instituting a special antenatal clinic to deal specifically with the problem (Beard and Roberts, 1970) but for this to be successful, all appropriate high risk patients must be selected for closer scrutiny. As discussed on page 25, there are major limitations in the risk assessment approach to the antenatal identification of the small-for-dates fetus, and this has been confirmed by our own experience (Neilson, 1979): A comprehensive list of at-risk criteria (Table 3 - 1) were applied retrospectively to the first 500 patients to be delivered in the Queen Mother's Hospital in 1977. It was found that 23% would have been included in the high-risk group and that 58% of the small-for-dates babies were born to these mothers. Exclusion of maternal age as a criterion reduced the high-risk group to more manageable proportions (16%) but only 43% of small-for-dates infants were then included.

TABLE 3 - 1

CRITERIA EMPLOYED IN EVALUATION OF RISK ASSESSMENT TO PREDICT SMALL-FOR-DATES INFANTS

1. EPIDEMIOLOGICAL FACTORS:

Maternal age	16 years
Maternal age	35 years

2. PREVIOUS REPRODUCTIVE HISTORY:

Previous small-for-dates infant
Previous stillbirth
Previous neonatal death
Previous placental abruption
Previous proteinuric pre-eclampsia

3. MATERNAL DISEASE:

Essential hypertension
Renal dysfunction
Diabetes mellitus

4. PREGNANCY COMPLICATIONS:

Moderate or severe pre-eclampsia
Antepartum haemorrhage

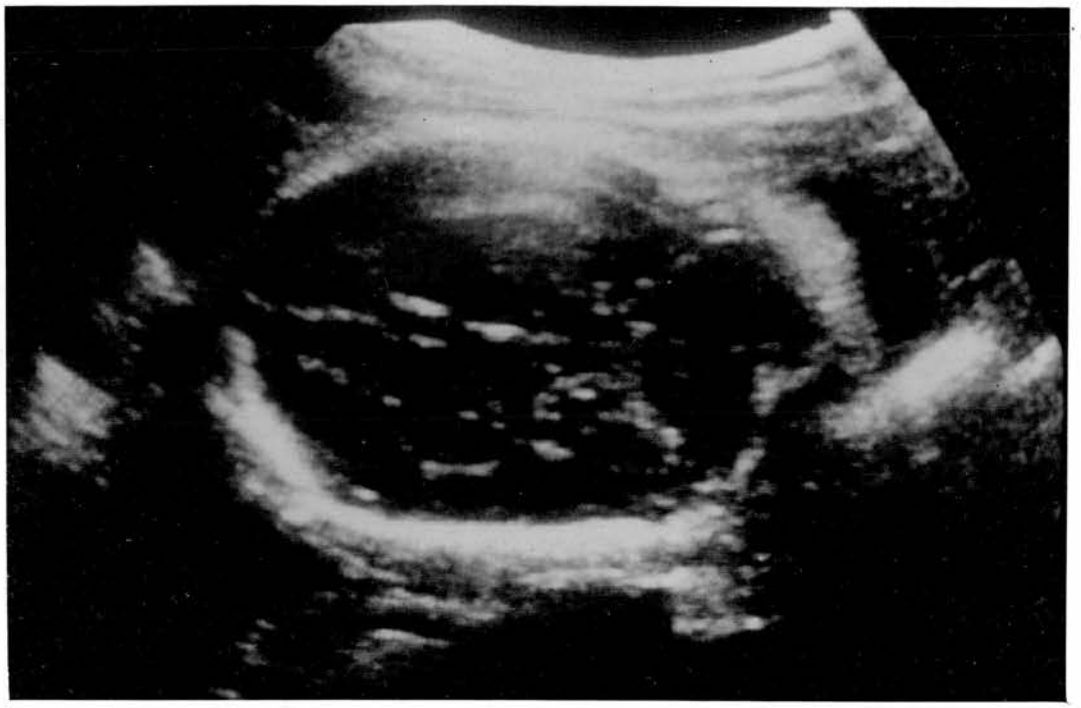
5. CLINICAL SUSPICION OF FETAL GROWTH RETARDATION

Ultrasound measurement of the fetus, which has been discussed in detail in the preceding chapter, would appear the ideal screening tool. The study described in this chapter aimed at the development of a means for screening for the small-for-dates fetus by a two-stage ultrasound examination schedule. The first-stage examination was an accurate assessment of gestational age in early pregnancy, the second an assessment of fetal size at between 34 and 36 weeks.

PATIENTS AND METHODS

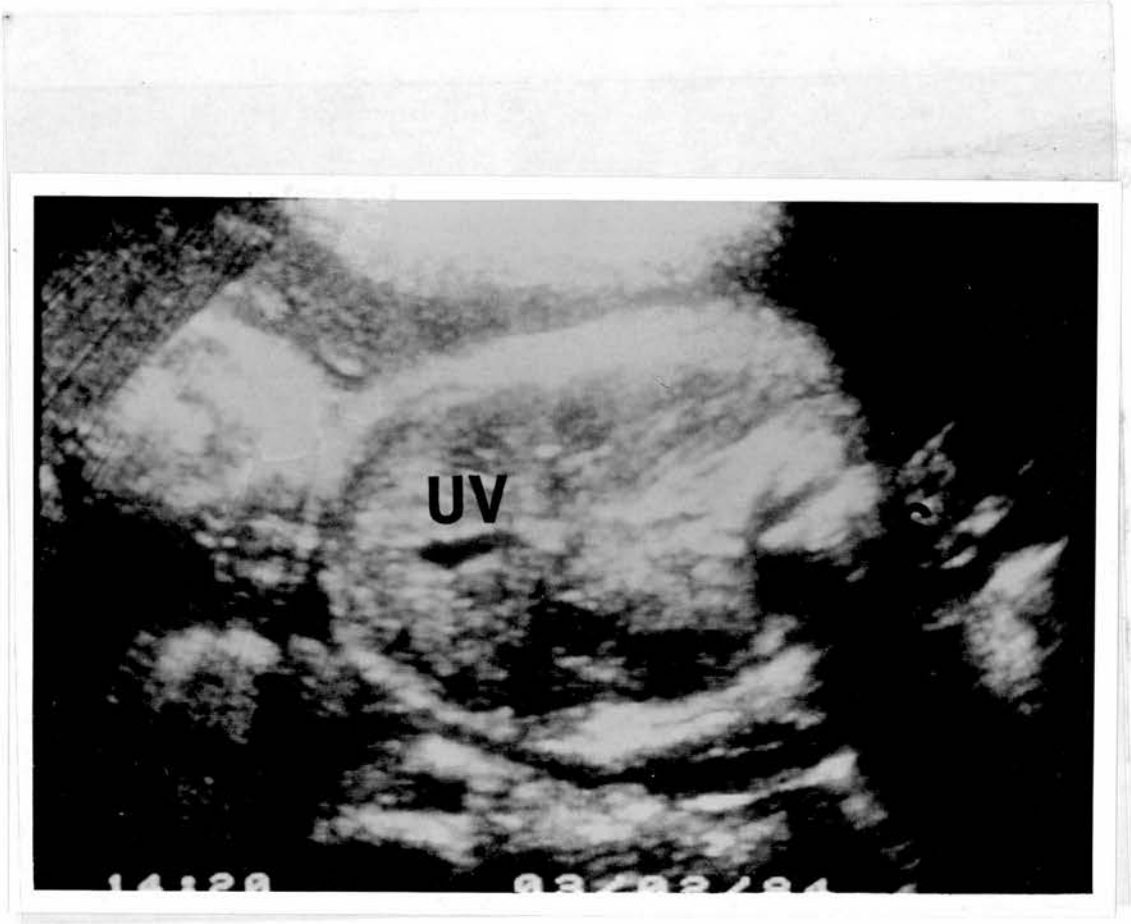
The study group comprised 474 patients with singleton pregnancies. Of these, 90 (19%) had been referred for serial biparietal cephalometry because of past or current pregnancy complications; the remainder were low-risk volunteers from the antenatal clinic. At any single session all patients attending the clinic whose pregnancy had advanced to between 34 and 36 weeks were asked to participate in the study, and less than 10% declined. All had undergone ultrasonic examination before 28 weeks, at their first visit to the antenatal clinic (in accordance with established hospital policy), when gestational age was assessed by measurement of fetal crown-rump length up to 14 weeks (Robinson, 1973), or the biparietal diameter, from 13 weeks (Campbell, 1969; 1976). Measurements were carried out in the antenatal clinic by a specially trained midwife or obstetrician using a real-time ultrasound scanner (System 85, Diagnostic Sonar, Livingstone, Scotland). When a discrepancy was found between ultrasound and clinical assessments of gestational age, the examination was repeated with a conventional static scanner in the diagnostic ultrasound department, and the result accepted as the definite indicator of gestational age. As a practical guide "discrepancy" was defined as a difference of more than one week at 6 to 15 weeks of pregnancy, more than one and a half weeks at 16 to 23 weeks, and more than two weeks at 24 to 28 weeks. If the patient was unsure of the date of the start of her last menstrual period or if other factors existed to make clinical assessment unreliable, the ultrasound assessment was always accepted as definitive. The mean gestational age at the time of this first-stage ultrasound examination was 15 weeks; 34% of the examinations were carried out before 14 weeks, 91% before 20 weeks, and all before 28 weeks.

Figure 3 - 1



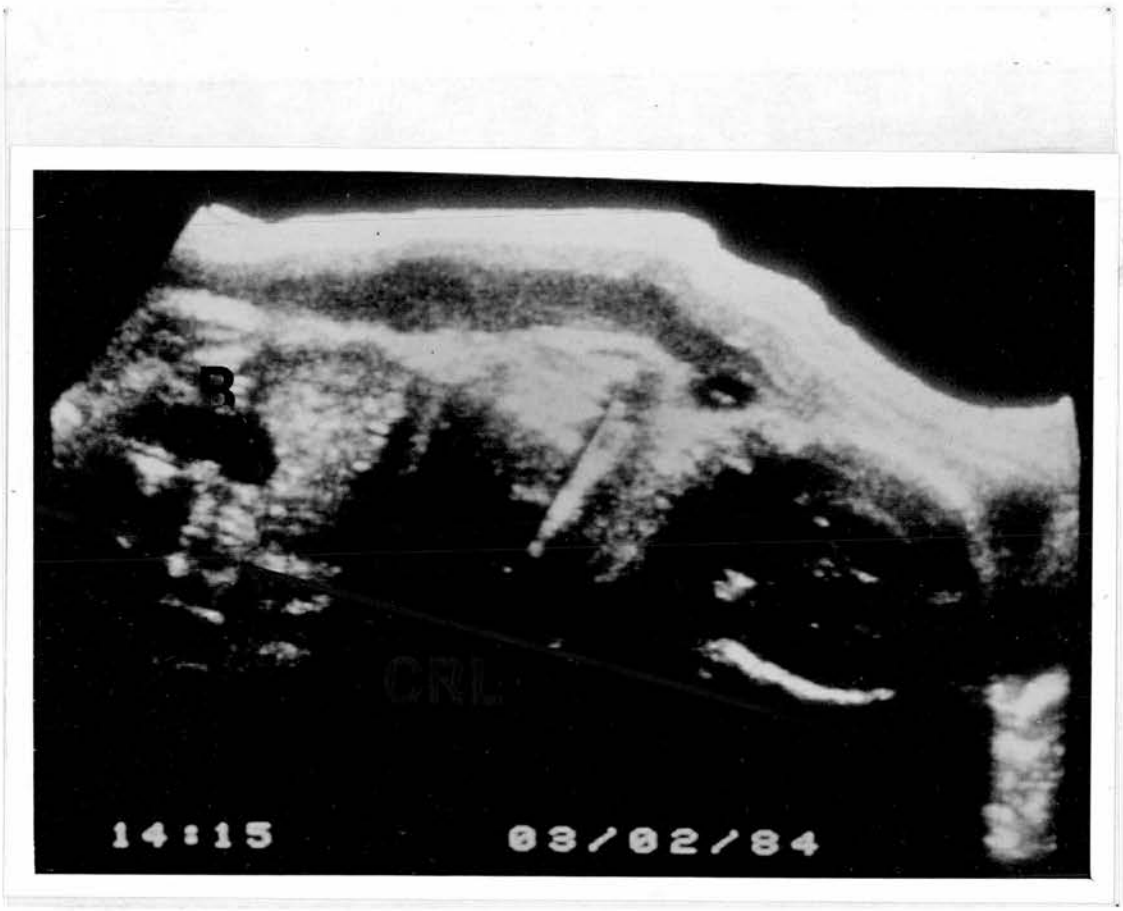
Ultrasonogram showing transverse section of fetal head.
SP : Septum pellucidum.

Figure 3 - 2



Ultrasonogram showing transverse section of fetal trunk.
UV : umbilical vein; S : fetal spine

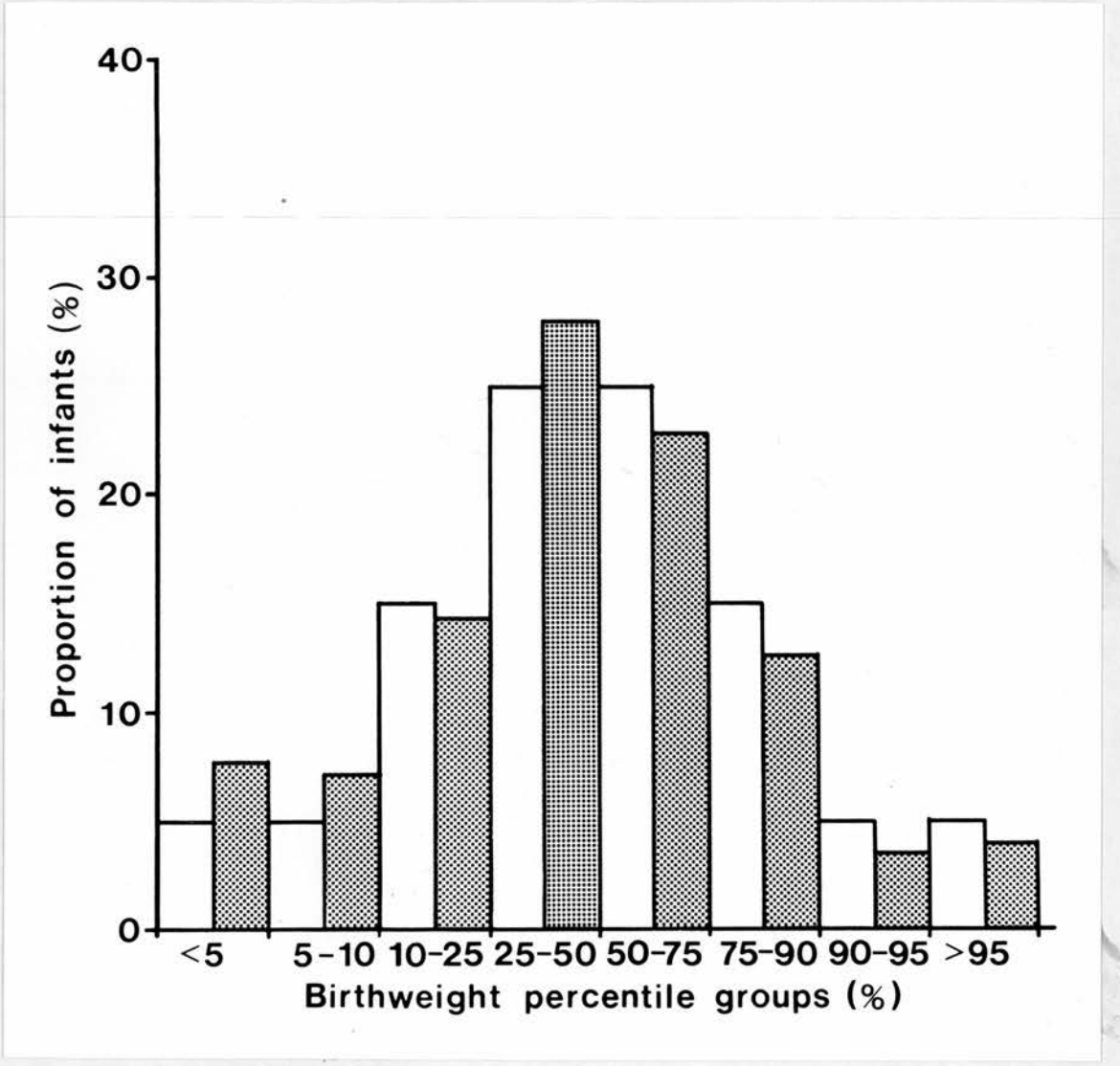
Figure 3 - 3



Ultrasonogram showing longitudinal section of fetus from which crown-rump length (CRL) is measured.
B : fetal bladder; H : fetal head.

It was planned that all second-stage examinations would be performed at between 34 and 36 weeks. Because, however, many patients had been asked to return to the antenatal clinic around 36 weeks and would not have been included in the study by strict adherence to this time period, the examinations were carried out between 238 days (34 weeks) and 255 days (36 weeks 3 days). The following fetal dimensions were measured : biparietal diameter (BPD), head area (HA), head circumference (HC), transverse trunk diameter (TTD), trunk area (TA), trunk circumference (TC), and crown-rump length (CRL). The BPD was measured by the combined A and B mode technique described by Campbell (1968); HA and HC were measured from a transverse ellipsoid section of the fetal head displaying a central midline echo (Falx cerebri) with a short double echo (septum pellucidum) one-third of the distance from the sinciput (Campbell and Thoms, 1977) Figure 3 - 1). Area, circumference and transverse diameter of the trunk were measured on a transverse section of the fetal trunk at right angles to the long axis of the aorta and displaying a short segment of umbilical vein (Campbell and Wilkin, 1975; Hansmann, 1977) Figure 3 - 2). The TTD was measured on the bistable display using electronic calipers calibrated to a velocity of 1600 m/s. CRL was measured on a longitudinal section of the fetus that included both the fetal bladder and the maximum area of the fetal head (Wittmann et al., 1979) (Figure 3 - 3); no allowance was made for flexion of the fetal trunk. A semi-automated electronic measuring device (page 43) was used for accurate and rapid measurement (direct from the grey-scale image) of area and circumference parameters and CRL (Fleming et al., 1978). All measurements were carried out by the author using a conventional static scanner (Diasonograph 4102,Nuclear Enterprises, Edinburgh). In 57 cases (12%) satisfactory head measurements could not be obtained, either because the fetal head was in a direct occipito-anterior or occipito-posterior position, or because it was low in the maternal pelvis. TA and TC were measured in all cases, as was CRL, a low fetal head being no obstacle to accurate measurement of this latter parameter.

Figure 3 - 4



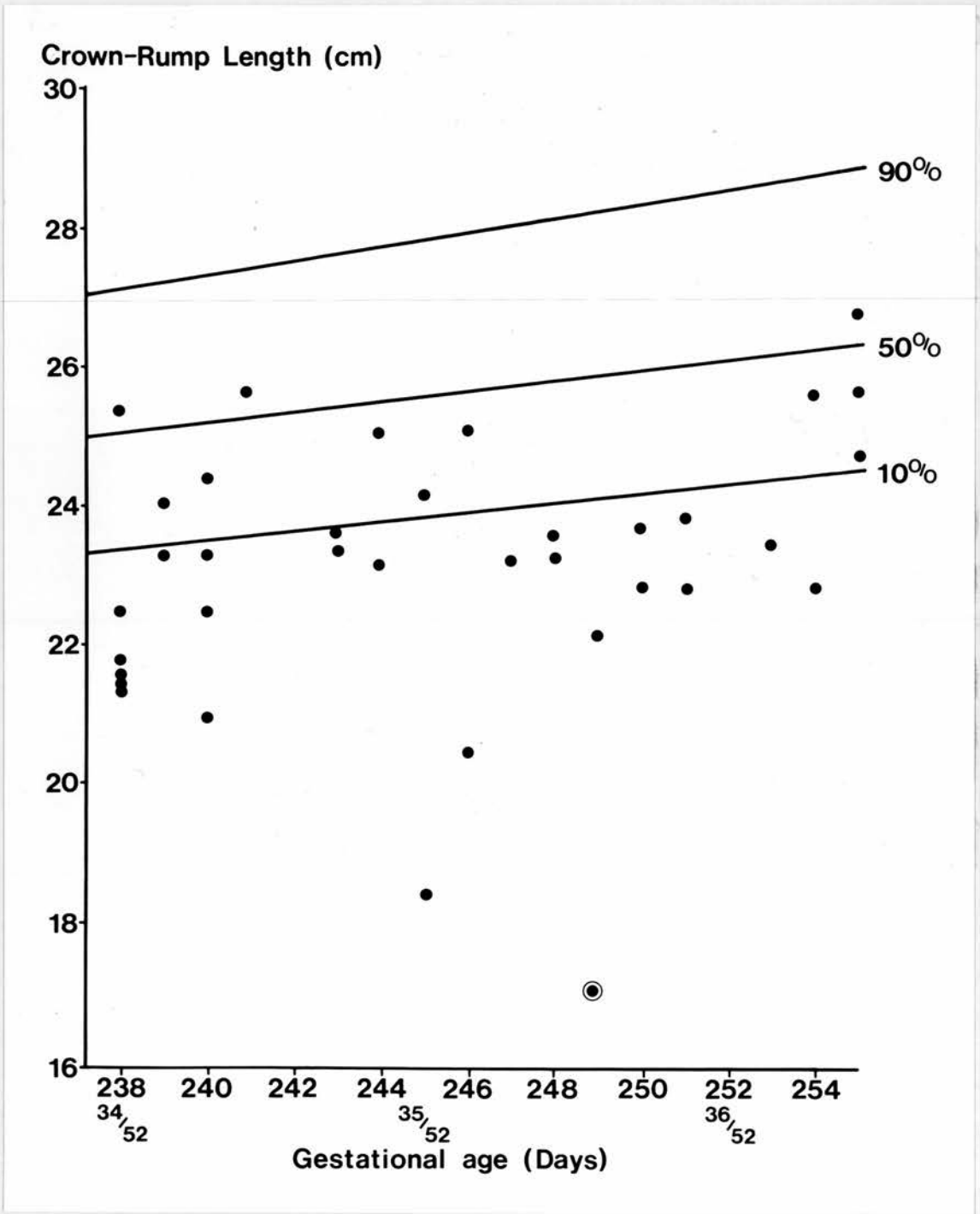
Histogram showing the birthweight distribution of the study babies (shaded columns) compared with that expected from the Aberdeen data (white columns).

After delivery the measured parameters were analysed, singly and in combination, to identify the optimal index for detecting small-for-dates fetuses. To this end, measurement and other relevant data were placed on computer cards. Nomograms were constructed by plotting for each parameter the measurements obtained from the babies of normal birthweight - that is, above the 5th percentile - against gestational age at the time of examination. Median, 10th and 90th percentile curves were constructed by plotting the appropriate values for each of the eight consecutive two-day periods between 238 and 255 days, and a smoothed percentile curve was obtained by carrying out a weighted least-squares analysis of the logarithms of the percentiles against time (the appropriate weights being the number of observations of the parameter in the relevant two-day period). Measurements obtained from the small-for-dates fetuses were then plotted and false-negative and false-positive rates calculated for each parameter, the 10th percentile curve on the nomograms being used as an arbitrary demarcation line for identifying small-for-dates fetuses. A false-positive result was recorded when the birthweight was normal though the measurement was below the 10th percentile curve, and a false-negative result recorded when the baby was small-for-dates though the measurement was above this demarcation line.

RESULTS

The birthweight distribution of the 474 babies is shown in Figure 3 - 4; 36 infants (7.6%) had birthweights on or below the 5th percentile of the Aberdeen chart (Thomson et al., 1968) and these were classified as small-for-dates. The mean birthweight in this group was 2.31 kg (range 1.20 - 2.77 kg) and it included two stillborn infants (both fresh), one of whom was the only malformed infant in the study (renal agenesis). The other infant died during an unsupervised vaginal breech delivery at home, the mother having declined hospitalisation. Of the 36 small-for-dates fetuses, 18 had not been suspected clinically as small-for-dates at any time, 17 were identified by abdominal palpation as small-for-dates, and in one case elective serial biparietal cephalometry provided evidence of growth retardation despite a clinical impression of normal growth.

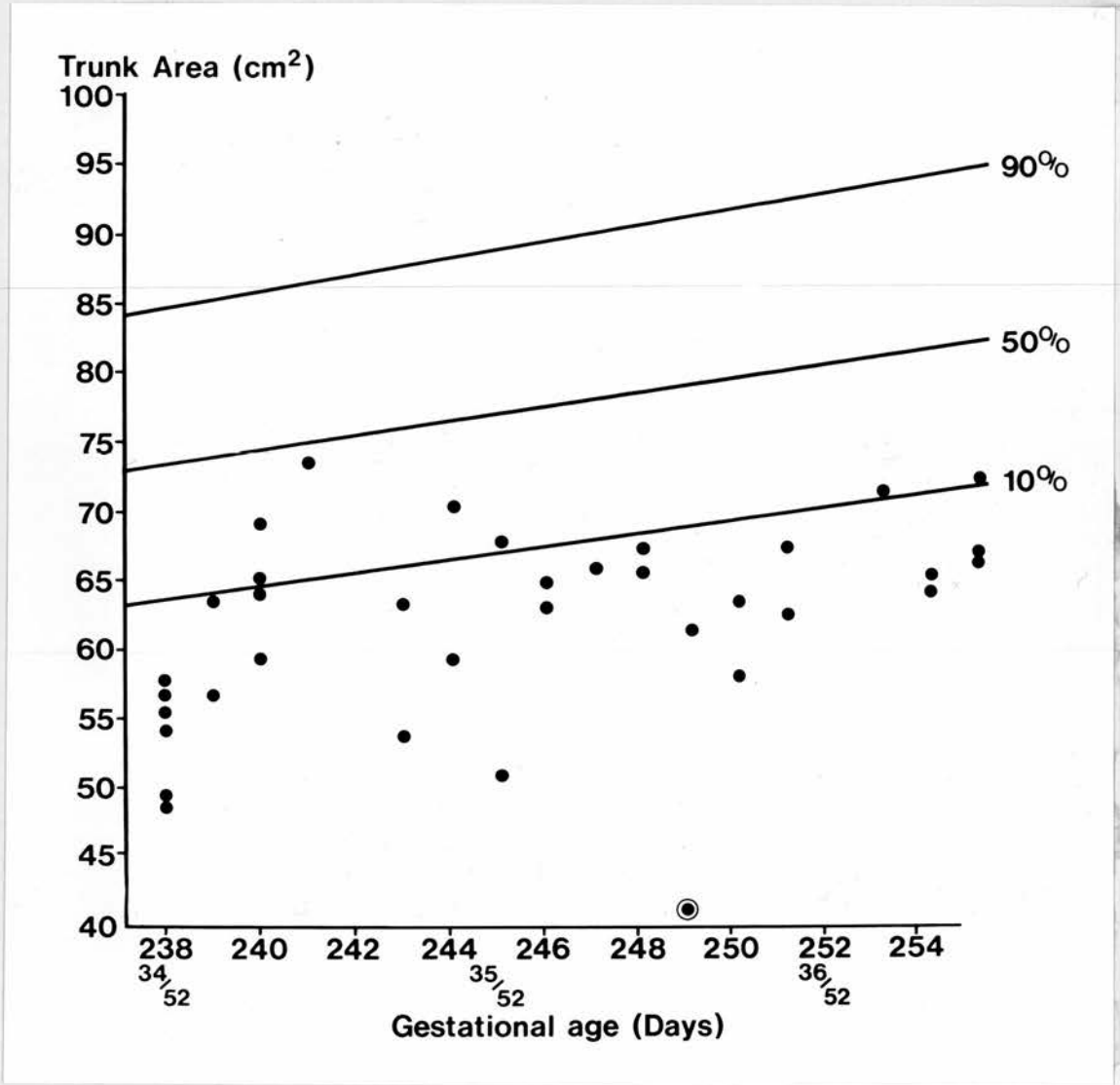
Figure 3 - 5



Crown-rump length measurements obtained from those fetuses that were small-for-dates at birth, plotted against gestational age at the time of measurement.

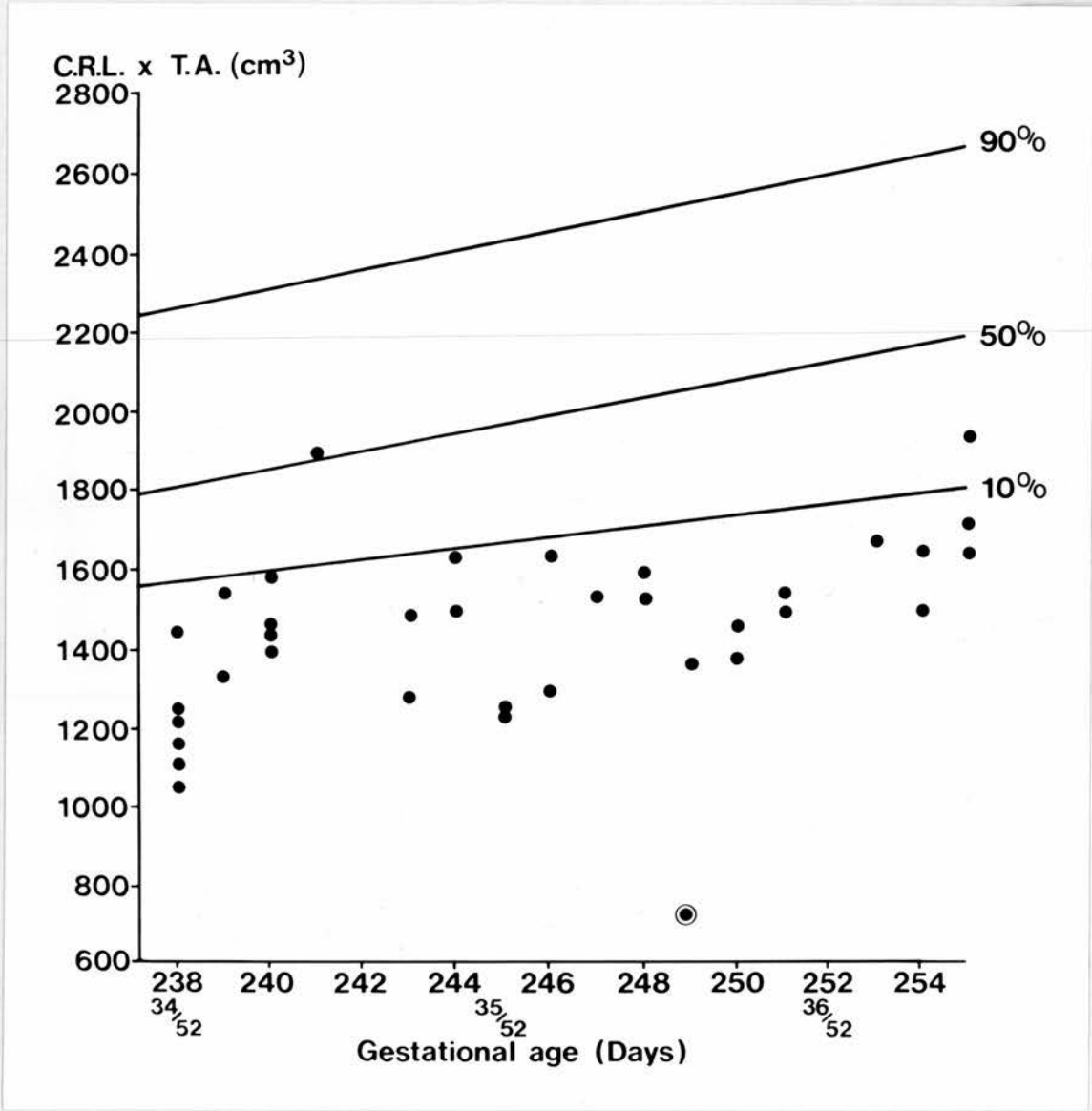
The encircled dot represents the fetus with renal agenesis.

Figure 3 - 6



Trunk area measurements obtained from those fetuses that were small-for-dates at birth, plotted against gestational age at the time of measurement. The encircled dot represents the fetus with renal agenesis.

Figure 3 - 7



Product of crown-rump length and trunk area (CRL X TA) : measurements obtained from those fetuses that were small-for-dates at birth, plotted against gestational age at the time of measurement. The 10th percentile curve is used as the demarcation line.

Prediction of babies that were small-for-dates at birth, by measurement of the different fetal parameters at second-stage examination are shown in Tables 3 - 2a and 3 - 2b. Head measurements (BPD, HA, HC) were insensitive screening examinations since they identified only 56 - 59 % of such babies. In contrast, measurement of the trunk parameters TA and TC correctly identified 81 % and 83 % respectively, although TTD with a sensitivity of 61 % was no more useful than the head measurements. Area and circumference measurements were extremely highly correlated with correlation coefficents between HA and HC and between TA and TC of, respectively, 0.994 and 0.995, and this is reflected in virtually identical efficacies. Similarly, the multiplication of TA and TC by CRL provided equivalently effective indices: the product of CRL and TA had a sensitivity of 94 % and specificity of 88 %; with the product of CRL and TC the sensitivity was 89 % and specificity 91 %.

As will be discussed later, the product of CRL and TA (CRL X TA) was selected for further study. The values obtained on small-for-dates fetuses with CRL, TA and CRL X TA measurements are demonstrated on Figures 3 - 5, 3 - 6 and 3 - 7; only two of the 36 affected fetuses were not identified by CRL X TA measurement. The false-positive rate obtained with this index was 12 % and the birth weight distribution of these 52 babies of normal birthweight is shown in Table 3 - 2c.

The ratio of HA to TA (Varma et al, 1979) gave a high false-negative rate.

TABLE 3 - 2a

PREDICTION OF BABIES THAT ARE SMALL-FOR-DATES (SFD) OR APPROPRIATE-FOR-DATES (AFD) BY MEASUREMENT OF DIFFERENT PARAMETERS AT SECOND-STAGE ULTRASOUND EXAMINATION.

	SFD			AFD		
Parameters	N	True Positive	True Negative	N	True Negative	True Positive
BPD	33	19	14	380	342	38
HA	33	19	14	381	342	38
HC	33	18	15	381	351	30
TA	36	29	7	438	390	48
TC	36	30	6	438	394	44
TTD	30	18	12	372	327	45
CRL	36	25	11	438	385	53
CRL x TA	36	34	2	438	385	52
CRL x TC	36	32	4	438	399	39
HA/TA	33	15	18	381	347	34

[In some cases, head measurements or TTD could not be measured due to fetal position]

TABLE 3 - 2b

SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES OF DIFFERENT POSSIBLE SCREENING EXAMINATIONS.

Parameter	Sensitivity %	Specificity %	Predictive Value Positive Result %	Predictive Value Negative Result %
BPD	58	90	33	96
HA	59	90	33	96
HC	56	92	38	96
TA	81	89	38	98
TC	83	90	41	99
TTD	61	88	29	96
CRL	69	88	32	97
CRL x TA	94	88	39	99
CRL x TC	89	91	45	99
HA/TA	44	91	31	95

TABLE 3 - 2c

BIRTHWEIGHT DISTRIBUTION OF BABIES WITH CRL x TA VALUES BELOW THE 10th CENTILE.

Birthweight	True Positive	False Positive
< 5 %	34	
5 - 10 %		23 (44 %)
10 - 25 %		14 (27 %)
25 - 50 %		12 (23 %)
50 - 75 %		3 (6 %)
75 - 90 %		0
90 - 95 %		0
> 95 %		0
	34	52

DISCUSSION

The aim of this study was the development of a procedure suitable for routine screening for small-for-dates fetuses and these have been defined as having a birthweight for gestational age, on or below the 5th percentile according to the charts of Thomson et al. (1968), which were based on the birthweights of over 52,000 infants born in Aberdeen between 1948 and 1964. These charts were chosen because of the extensive nature of the Aberdeen study and also because of the geographical proximity of Aberdeen to Glasgow. There are, however, socio-economic and population differences between these two Scottish cities and, since completion and analysis of the studies reported in this thesis, birthweight for gestational age standards have been reported for the Glasgow population (Forbes and Smalls, 1983). Comparison of the Aberdeen and Glasgow birthweight values at the 5th percentile is shown in Table 3 - 3; the differences were greater for pre-term births and the average difference from 37 weeks, when the large majority of infants in the study reported here were delivered, was only 40 g. Various workers have used different criteria to define the small-for-dates infant; these have included 10th and 5th percentiles and minus two standard deviations from the mean. The 5th percentile was chosen for this study both because it corresponds to the criteria used by Campbell who has carried out the most important innovative research into ultrasound assessment of fetal growth, and also because it includes those fetuses most at risk from intrauterine growth retardation. Thus Dobson et al (1981), in a study of 500 infants with birthweights less than the 10th percentile, found the perinatal mortality rate among those with birthweights less than the 5th percentile to be 190/1000; those with birthweights less than the 10th percentile but greater than the 5th percentile had a perinatal mortality rate of 22/1000, and controls of normal birthweight had a rate of 11/100. The latter two figures were not statistically different.

In the study reported here, sex and parity (Thomson et al.,1968) were not taken into account in making the diagnosis of small-for-dates. The lower average birthweight in first pregnancies, compared with

TABLE 3 - 3

COMPARISON OF BIRTHWEIGHTS AT THE 5TH PERCENTILE BETWEEN ABERDEEN AND GLASGOW POPULATIONS, FROM 32 TO 42 WEEKS.

Gestational age (weeks)	Birthweight Aberdeen* (grams)	Birthweight Glasgow** (grams)
32	1170	1090
33	1460	1320
34	1730	1560
35	1970	1800
36	2180	2030
37	2360	2250
38	2510	2450
39	2640	2610
40	2740	2730
41	2800	2800
42	2840	2810

(Data from Thomson et al. (1968)* and Forbes and Smalls (1983)**)

second and subsequent pregnancies, must be assumed to be due to an environmental restriction of fetal growth and unless this is proved to be innocuous (and perinatal mortality rates are higher in first than second pregnancies) it is illogical to make allowances for parity in studies such as this. The same applies to maternal height and weight, corrections advocated by Tanner and Thomson (1970). The possible reasons why male infants are heavier than females have been discussed in Chapter 1, and this does not seem to result in increased risk to female infants. However, if sex is taken into account to define small-for-dates this would require, for the sake of consistency, separate ultrasound growth charts, and ultrasound values could not be evaluated because fetal sex is unknown, before delivery, in the large majority of pregnancies. For these reasons and for the sake of simplicity, small-for-dates infants have been defined by birthweight on or below the 5th percentile for gestational age without "correction" for sex, parity, maternal height and weight.

The screening procedure described in this study comprises a two-stage ultrasound examination schedule, an accurate knowledge of gestational age being essential to permit interpretation of the second-stage examination result because major errors may occur in the clinical estimation of gestational age, even in the first trimester (Beazley and Underhill, 1970). In the Queen Mother's Hospital, the first-stage examination is incorporated into a routine policy of carrying out ultrasound examinations on all patients at their first attendance at the antenatal clinic when assessment of gestational age is most accurate. Additional advantages of this policy include detection of multiple pregnancies, non-viable pregnancies and some fetal abnormalities (Neilson and Hood, 1980). Real-time ultrasound scanners have been shown to allow accurate measurement of CRL during the first trimester (Adam et al., 1979) and of BPD during the second trimester (Adam et al., 1978; Osinusi et al., 1980), and, using these equipments, the procedure may be easily assimilated into the smooth running of the antenatal clinic.

The timing of the second-stage examination at 34 to 36 weeks also requires comment. At any gestational age, fetuses of similar size may be growing, and thereafter continue to grow, at different rates. Hence, if any ultrasound measurement has validity as an index of fetal size its accuracy in predicting birthweight and identifying small-for-dates fetuses increases as the time interval between measurement and delivery decreases; this is logical and it has been substantiated on prospective study by Wittman et al (1979). Thus, the sensitivity of detection of small-for-dates fetuses would be expected to be greater at, for example, 40 weeks than 30 weeks. However, the clinical value of this information decreases as pregnancy advances because at each week of pregnancy intrauterine deaths accumulate as a result of fetal growth retardation and increasingly less time is available for institution of tests of fetal wellbeing among the rest. The time period of 34 to 36 weeks, chosen for this study, represents a compromise between efficiency in detecting small-for-dates fetuses and the usefulness of the information provided. As discussed earlier, Usher and McLean (1974) have estimated that 70% of perinatal deaths associated with fetal growth retardation in Montreal could be avoided by accurate identification of small-for-dates fetuses at 34 weeks, and McIlwaine et al. (1979) found that 45% of intrauterine deaths associated with fetal growth retardation in Scotland occurred after 36 weeks. Another point of relevance is that neonatal mortality among small-for-dates infants decreases enormously as pregnancy advances; Lubchenco et al. (1972) found that while the neonatal mortality rate of infants born at 32 weeks and weighing between 1000 g and 1250 g was 400/1000, that of the equivalent small-for-dates group at 38 weeks (2000 g to 2250 g) was 40/1000, ten-fold less. The combination of fetal growth retardation and prematurity is associated with high neonatal mortality; small-for-dates infants born in good condition at term do well and it is some of these infants which will be missed by screening earlier than 34 weeks. Wittmann et al. (1979) found that measurement of CRL X TA between 32 and 34 weeks correctly identified only 8 of 14 small-for-dates fetuses (57%); between 34 and 36 weeks, 10 of 12 (83%) were detected.

In the study described here, the head measurements were generally less efficient as second-stage parameters than were the trunk measurements, reflecting the brain-sparing effect in which brain weight is relatively less diminished than liver weight in small-for-dates fetuses (Gruenwald, 1974). TTD, however, was less efficient than the other trunk measurements; in small-for-dates fetuses the transverse trunk section is often distorted from the usual near-circular shape and may be elongated in either the anteroposterior or transverse plane. With transverse elongation of the trunk the diameter may be within normal limits despite reduced TA and TC.

Slightly higher sensitivities were obtained by the product of CRL and TA or TC than by measurement of the trunk parameters alone, although, because of the relatively small number of small-for-dates babies in this study, no meaningful formal statistical evaluation could be made of the relative efficacies. Small-for-dates infants have shorter body lengths (Usher and McLean, 1974) and measurement of the direct CRL is also of value in aiding detection of the hyperflexed small-for-dates fetus. In addition, flexion on the fetal trunk not only decreases the measured CRL, but probably also increases the dimensions of the measured transverse section, so that a combination of length and cross-sectional area provides a better assessment of fetal size. Little and Campbell (1982) have criticised, on theoretical grounds, CRL measurement as performed in this study - that it is "unphysiological" because it does not represent the true fetal crown-rump length, and that the exact point at which the rump ends is often poorly defined because of maternal bowel gas overlying the fundus of the uterus or the apposition of the rump to the uterine wall or placenta. In reply, it may be said that the aim of the study was not the assessment of physiological growth of the fetus, but the development of a practical means of screening for the small-for-dates fetus. Measurement of true crown-rump length would take longer (a practical disadvantage) and would appear to have theoretical disadvantages in aiding detection of the small-for-dates fetus, as outlined above. The different acoustic characteristics of fetal tissue on one hand and placenta and uterus on the other means that the end point of the rump may be readily detected; overlying maternal bowel gas does not pose a practical problem in the experience of the author who has found the only situation where definition of the rump may be difficult, is when the fetal hips are extended, and this is rare.

The 10th percentile curve for each parameter measured on normally grown fetuses was chosen arbitrarily as a means of comparing the usefulness of the different parameters, and as a possibly useful demarcation line bearing in mind the excessive presence of babies of lower birth weight as a result of the selection of subjects. As a means for detecting the small-for-dates fetus, the demarcation line need not have been a percentile curve and it would have been quite justifiable to have drawn a suitable demarcation line with a ruler at the completion of the study. Although the 10th percentile curve was calculated and plotted in identical fashion for each parameter, there was some small variation in the false-positive rate as a result of differing distributions of values. In this context, false-negative and false-positive results should not be given equal weight. The author is in agreement with Stempel (1982) that in any procedure which is advocated as a means for detecting the small-for-dates fetus, false-negative results are of greater significance than false-positive results. Intervention is planned predominantly on the results of tests of fetal wellbeing and normally grown fetuses in good condition but with low ultrasound values may thus be managed conservatively. On the other hand, the false reassurance that a small-for-dates fetus is of normal size leads to obvious dangers. This is in contrast to, for example, a prenatal test to detect a lethal fetal abnormality with which it is vital to avoid false-positive reports, even at the cost of diminished sensitivity, so that normal fetuses are not, in consequence, aborted. The clinical context and therapeutic implications are of cardinal concern in balancing optimal sensitivity against specificity for any diagnostic test.

Of the several measurements which effectively identified small-for-dates fetuses, CRL x TA was selected for further study. Area measurement is <u>theoretically</u> more accurate than circumference measurement using the particular equipment utilised for these studies, (Fleming et al, 1978) - on electronic "tracing" of the outline of a fetal section, the trace will inevitably deviate from the actual outline; if, for each sector measured, the trace equally deviates within and without the boundaries, area measurement will be accurate whereas circumference will be overestimated. This is probably only of theoretical concern, however, because (as described earlier) TA and/

and TC were found to be extremely highly correlated (r = 0.995) and the efficacies of CRL x TA and of CRL x TC on one hand, and of TA and of TC on the other, were virtually identical.

CRL x TA was preferred to TA alone because of its possibly increased sensitivity. Despite the disadvantage of performing two rather than one measurement, in the author's hands, using the semi-automated area and perimeter device, the entire procedure, including plotting of the result and explanation to the mother, took about four minutes. It was thus logistically suitable as a screening procedure. The efficacy of CRL x TA measurement did, however, require prospective assessment, and studies designed to evaluate this are described in the following two chapters. The 12% false-positive rate found in this study must not be ignored since an erroneous diagnosis that the fetus is small-for-dates may lead occasionally to inappropriate intervention; Chapter 4 describes a prospective randomised controlled trial to assess the possible positive or negative effects on fetal outcome and obstetric management of instituting this screening programme in low-risk patients.

With a sensitivity of 94%, specificity of 88% and predictive value of 39%, the 10th percentile curve calculated for CRL x TA proved so suitable that analysis of alternative demarcation lines appeared superfluous.

CHAPTER 4.

SCREENING FOR THE SMALL-FOR-DATES FETUS: A PROSPECTIVE RANDOMISED CONTROLLED TRIAL

INTRODUCTION

The study reported in the preceding chapter showed that the two-stage ultrasound examination schedule, comprising assessment of gestational age in early pregnancy followed by measurement of the product of crown-rump length and trunk area (CRL X TA) at 34 to 36 weeks, appeared highly effective in the detection of the small-for-dates fetus and seemed suitable as a screening procedure. The study reported in this chapter describes the use of this schedule in a group of patients not thought to be at high risk of producing a small-for-dates infant. The aims of the study were two-fold:

(i) to evaluate prospectively the efficacy of CRL X TA measurement in detecting small-for-dates fetuses;

(ii) to assess the impact on fetal outcome and obstetric management of instituting the two-stage schedule in "low-risk" mothers.

On the first point, the preceding chapter described how the seven fetal parameters, measured at 34 to 36 weeks, were evaluated as indices of fetal growth retardation at the completion of the study. It is obvious that the results of CRL X TA measurement obtained thus, may not necessarily correspond to those found on prospective study.

The second aim addresses the question of whether, assuming CRL X TA measurement is confirmed to be effective, this screening procedure leads to an improvement in fetal outcome and, if so, whether this is to such an extent that it justifies implementation as a routine. The facts that small-for-dates fetuses demonstrate high perinatal mortality and morbidity, and that CRL X TA measurement appears highly effective in detecting such fetuses, do not necessarily mean that introduction of routine measurement would be advantageous. Should the outcome for small-for-dates fetuses be improved, this could, for example, be outweighed by the effects of inappropriate intervention in pregnancies in which a false-positive diagnosis of growth retardation had been made.

Many techniques of fetal assessment were introduced into obstetric practice during the 1960's and 1970's but none were evaluated by means of prospective randomised controlled trials prior to their introduction.

Of those that have now been so evaluated, e.g. oestrogen (Duenhoelter et al. 1975) and HPL (Spellacy et al., 1975) assay, antepartum cardiotocography (Brown et al., 1982; Flynn et al., 1982) and continuous fetal heart rate monitoring during labour (Renou et al., 1976; Kelso et al., 1978; Haverchamp et al., 1979), assessment was not made until after these techniques already enjoyed a well established place in obstetric practice. Under such circumstances assessment becomes more difficult for "ethical" and practical reasons, and the rationalisation of the use of a procedure already accepted in clinical practice is often impossible. Chalmers et al. (1976a), in a retrospective study in Cardiff, were unable to demonstrate any difference in perinatal mortality and morbidity between two obstetric teams, only one of which enthusiastically employed oestriol assays and ultrasonic biparietal cephalometry in fetal assessment. To quote these workers:

> "suggestions that either urinary oestrogen assay or serial ultrasound cephalometry will only pay perinatal dividends when total population screening is employed must be evaluated in exactly the same way as their use in a selected population - by controlled trial .... Our own research has shown us that we are in urgent need of experimentally-derived information with which to plan a rational deployment of our limited resources."

(Chalmers et al., 1976b).

The results of carrying out CRL X TA measurement were assessed, in the study reported here, by means of a prospective randomised controlled trial. Only low risk patients were studied because:

(i) approximately half of small-for-dates infants are born to these mothers,

(ii) non-clinical techniques of fetal assessment are not, currently, applied in these pregnancies to aid detection of the small-for-dates fetus,

(iii) it would be unethical and impractical to attempt to withhold relevant information in high-risk pregnancies where concern about fetal wellbeing pre-existed.

PATIENTS AND METHODS

The study was carried out between May 1979 and January 1981. Suitable subjects were identified by the inspection of case records on the day prior to each hospital antenatal clinic. Patients whose pregnancies had

advanced to between 238 days (34 weeks) and 255 days (36 weeks 3 days) gestational age at the time of antenatal clinic attendance, and who did not fall into any of the exclusion categories listed below, were asked to participate in the study. The format of the study had been approved by the hospital ethical committee and informed consent was obtained from each subject. Whilst no formal record was kept of the number of patients who declined to participate in the study, it is estimated that approximately 90% of those asked, participated. Ultrasound examination was performed immediately after antenatal clinic attendance.

Deliberate exclusions from the trial will be discussed along with reasons why suitable patients were not requested to participate:

(i) Uncertain gestational age

Because of the uncertainties associated with clinical assessment of gestational age, it was thought vital to carry out ultrasound examination in early pregnancy to accurately pin-point gestational age as a reference point for interpretation of CRL X TA measurement. This first-stage examination was performed on all patients when they first attended the antenatal clinic, gestational age being assessed by measurement of the fetal crown-rump length up to 14 weeks (Robinson, 1973) and of the biparietal diameter after 13 weeks (Campbell, 1969; 1976). When a discrepancy existed between clinical and (repeated) ultrasound assessment of gestational age, the ultrasound dates were accepted (see Chapter 3). As discussed earlier, the accuracy of ultrasound measurement as an index of gestational age decreases as pregnancy advances. For the purposes of this study, 24 weeks were regarded as the maximum gestational age at which ultrasound examination was of sufficient accuracy to constitute the first-stage examination. Patients who, through late attendance at the antenatal clinic, did not undergo ultrasound examination before 24 weeks, were ineligable for inclusion in the study.

(ii) High-risk patients

Patients deemed to be at high risk of producing a small-for dates infant were excluded. The decision of the relevant clinical staff as to which of their patients were high risk was accepted. Thus were excluded:

(a) any patient in whom biochemical and/or biophysical (including ultrasound) monitoring had been initiated because of an unfavourable previous reproductive history or the development of complications during the current pregnancy;

(b) any patient in whom clinical suspicion of fetal growth retardation had already been recorded,

(c) any patient for whom the clinical staff had requested the results of CRL X TA measurement on the day of the second-stage examination.

(iii) Multiple pregnancies

Multiple pregnancy is associated with a high perinatal mortality rate (McIlwaine et al., 1979b) and a high incidence of fetal growth retardation (Manlan and Scott, 1978). Patients with multiple pregnancy should be regarded as being at high risk of producing small-for-dates infants and they were, therefore, excluded from this study. The use of CRL X TA measurement in twin pregnancies was, however, evaluated separately and the results are presented in Chapter 6.

(iv) Peripheral clinic patients

There are six antenatal clinics held each week in the Queen Mother's Hospital. An additional two antenatal clinics, staffed by hospital obstetricians, are held in a large housing estate on the outskirts of Glasgow, Drumchapel. Patients who attend the Drumchapel clinics (13% of the total) are delivered in the Queen Mother's Hospital but all normal aspects of antenatal care (including early ultrasound examination) are performed at the local clinic. For practical and financial reasons it was not thought reasonable to ask these patients to travel

to the hospital for participation in the study. It is however, worthy of note that the Drumchapel population contains a higher proportion of women of social classes 4 and 5, and produces a higher proportion of small-for-dates infants than the population attending the antenatal clinics at the hospital. (Ridley : personal communication).

(v) Failure of attendance at 34 to 36 weeks

There is no rigid scheme of timing visits to the antenatal clinics; some patients were not asked to attend at a time when they would have been within the screening period of 34 to 36 weeks, and they were therefore ineligible for inclusion in the study as were patients who defaulted from attendance at the relevant time.

(vi) Miscellaneous

(a) As discussed previously, patients were under no obligation to participate in the study and some declined to do so.

(b) On several occasions either the static ultrasound scanner (which was rather old) or the electronic area and perimeter measuring device ceased to function leading to the cancellation of study sessions.

(c) Clinical and other commitments (including holidays) of the author and his collaborator meant that not all available sessions were utilised.

The study group comprised 879 patients. All had undergone first-stage ultrasound examination before 24 weeks (mean 14.0 weeks S.D. 3.1). At the time of entry into the study all had apparently normal singleton pregnancies without clinical evidence of fetal growth retardation. At the time of second-stage ultrasound examination at 34 to 36 weeks, subjects were randomly allocated to one of two groups according to whether the last digit of their hospital number was odd or even (this was alternated monthly). In both groups fetal CRL and TA were measured by the technique described in Chapter 3. In group 1 subjects (reported group), the product CRL X TA was calculated, the best assessment of gestational age was made, the CRL X TA value was plotted on the chart obtained from the Chapter 3 study, and the chart inserted into the case-notes.

To ensure that the clinical staff were aware that their patient had been included in the study, the antenatal sheet was prominently stamped with the words "IUGR Study", and a written interpretation of the CRL X TA value was included on the ultrasound report sheet in the case-notes. If the CRL X TA value fell on or below the demarcation line (the 10th percentile curve), the written report indicated that "this may represent fetal growth retardation", and arrangements were made for the patient to return to the antenatal clinic the following week (if not previously so arranged). In some such cases repeated CRL X TA measurement was performed at that time. Otherwise subsequent management and fetal monitoring were left entirely to the clinical staff.

In group 2 patients (non-reported group), the CRL and TA were recorded on project sheets, without calculation of the product or interpretation of the results. The antenatal sheet was stamped as in group 1, and the ultrasound report sheet was stamped "not reported". There were, thus, two groups of subjects - those in whom the CRL X TA values were reported to the clinical staff, and those in whom the clinical staff were unaware of the CRL X TA value. All second-stage ultrasound examinations were performed by the author or by Dr. S.P. Munjanja.

Whilst there is no uniformity of opinion as to which factors are significantly associated with fetal growth retardation (McKeown and Gibson, 1951; Love and Kinch, 1965; Scott and Usher, 1966; Hedberg and Holmdahl, 1970; Galbraith et al., 1979), those characteristics that have been described as important were recorded during the study; these included maternal age, height and weight, parity, cigarette consumption, social class and race. Many of these factors also correlate with overall perinatal mortality (Baird, 1963; McIlwaine et al., 1979). Also recorded were the subsequent development of pregnancy complications such as hypertension and antepartum haemorrhage, and the consequent need for admission to hospital. Details of delivery and the sex, birthweight and condition at birth of the babies were also recorded. Condition at birth was assessed by the scoring system of Apgar

(Apgar and James, 1962) at one and five minutes. Whilst accepting that the correlation between Apgar score and metabolic acidosis is not good (Sykes et al., 1982), it was felt that Apgar scoring was sufficiently sensitive for the purposes of this study. Although almost all patients underwent continuous fetal heart rate monitoring during labour, no attempt was made to calculate the incidence of fetal distress during labour because of disparity of opinion as to what constitutes fetal distress (Steer, 1982) and how it should be managed. What is more important than the author retrospectively analysing intrapartum cardiotocographic traces, is the reaction of the clinical staff to the traces within the whole clinical setting of the patient in labour.

In several cases there had been incomplete documentation of data in the case-notes (e.g. maternal height had not been recorded). In others the case-notes were missing at the time of analysis of outcome and in these patients the Labour Ward records were used. These provided most but not all of the required information and this accounts for the small inconsistencies in some of the tabulated numbers.

Data on group characteristics and on fetal outcome and obstetric management were recorded on computer cards, and statistical evaluation was performed using the Statistical Package for the Social Sciences (SPSS). The two statistical tests used to examine inter-group differences were the chi-squared test and the t test for independant samples. The former was used when the data was categorical in nature; the latter was employed when the data displayed an interval level of measurement and when the variances of the samples did not differ significantly. When the F ratio test indicated a significant difference in the variances, a modified form of the t test, in which sample variance was separately estimated, was used (see SPSS manual).

The characteristics of both groups of subjects are shown and compared in Table 4 - 1; the only significant inter-group difference was in social class distribution (x^2 11.74, 4df, $P < 0.05$) with more social class 5 patients in the reported group. It is particularly difficult to identify those nulliparous patients who are at high risk of

TABLE 4 - 1

CHARACTERISTICS OF SUBJECTS GROUPED ACCORDING TO WHETHER THE CRL X TA VALUE WAS REPORTED (GROUP 1) OR NOT (GROUP 2).

Where appropriate mean values and one standard deviation, or numbers and percentages are tabulated.
Statistical comparison between the two groups was by X^2 or t tests.
(N.S. = no significant difference).

	GROUP 1 (REPORTED)	GROUP 2 (NOT REPORTED)	
1. Number	433	444	
2. Maternal Age (yrs)	27.3 (SD 5.1)	27.4 (SD 4.9)	N.S.
3. Maternal Height (cms)	160.5 (SD 6.3)	160.8 (SD 5.9)	N.S.
4. Maternal Weight (34-36 weeks)(kg)	69.1 (SD 10.4)	69.4 (SD 9.4)	N.S.
5. Social Class I	40 (9%)	39 (9%)	$p < 0.05$
II	108 (25%)	111 (25%)	
III	139 (32%)	185 (42%)	
IV	86 (20%)	73 (16%)	
V	56 (13%)	36 (8%)	
6. Race: White	406 (94%)	427 (96%)	N.S.
Asian	17 (4%)	12 (3%)	
Other	8 (2%)	5 (1%)	
7. Smoking: None	313 (73%)	321 (73%)	N.S.
< 10/Day	41 (10%)	45 (10%)	
10 - 20/Day	53 (12%)	53 (12%)	
> 20/Day	23 (5%)	21 (5%)	
8. Nulliparas	190 (46%)	178 (40%)	
9. No. of Previous Pregnancies: 0	165 (40%)	157 (35%)	N.S.
1	137 (33%)	147 (33%)	
2	59 (14%)	90 (20%)	
3	32 (7%)	30 (7%)	
4	22 (5%)	20 (5%)	
10. Blood Group 0	230 (56%)	243 (56%)	N.S.
A	129 (31%)	132 (30%)	
B	42 (10%)	46 (10%)	
AB	13 (3%)	15 (3%)	
11. Consultant 1	86 (20%)	94 (21%)	N.S.
2	68 (16%)	67 (15%)	
3	78 (18%)	87 (20%)	
4	91 (21%)	95 (21%)	
5	65 (15%)	57 (13%)	
6	44 (10%)	44 (10%)	
12. Gestational Age 1st-stage ultrasound (weeks)	14.1 (SD 3.1)	14.0 (SD 3.1)	N.S.
13. Serum AFP: Normal	349	347	N.S.
High	3	1	
14. 2nd Trimester Amniocentesis	30 (7%)	29 (7%)	N.S.

producing a small-for-dates infant because reproductive performance is unknown (Adelstein and Fedrick, 1978; Galbraith et al., 1979); the characteristics of the nulliparous subjects in both groups were therefore further compared (Table 4 - 2). This analysis showed that the difference in social class distribution was confined to parous subjects (x^2 13.29, 4 df, $p < 0.01$) but among the nulliparas, there was a significant difference in fetal presentation at the time of second-stage ultrasound examination (x^2 4.74, 1 df, $p < 0.05$) due to a greater incidence of breech presentation in the non-reported group. These sub-groups were otherwise similar.

The details of findings at second-stage examination are shown in Table 4 - 3. On nine occasions clinically unsuspected breech presentation was identified at second-stage ultrasound examination. A single case of unsuspected major placenta praevia was also discovered. These findings were always reported to the clinical staff regardless of to which group the patient had been allocated.

The clinical staff were entitled to obtain CRL X TA results of Group 2 subjects if this appeared important at any time after measurement; this never occurred and there were no exclusions for this reason. Two subjects from Group 1 were, however, excluded because they delivered elsewhere; in both cases the CRL X TA value was normal. Thus, in the study there were 877 singleton babies delivered. All babies were liveborn although one very large infant (birthweight 5.32 kg) in Group 1 had an Apgar scope of 0 at one minute following shoulder dystocia, but was successfully resuscitated and has appeared normal at paediatic follow-up. Those babies with birthweights equal to or less than the 5th percentile of the Aberdeen chart (Thomson et al., 1968) were classified as small-for-dates, and these numbered 33 (3.9%). There were two babies with major malformations, both from Group 2 mothers. One was an Amsterdam dwarf (Cornelia - de - Lange syndrome), and the other a baby with open lumbar spina bifida and microcephaly. The latter infant died as a neonate and this was the only perinatal death in the study (perinatal mortality rate 1.1/1000). The diagnosis of microcephaly was suspected at second-stage examination; this

TABLE 4 - 2

CHARACTERISTICS OF NULLIPAROUS SUBJECTS GROUPED ACCORDING TO WHETHER THE CRL X TA VALUE WAS REPORTED (GROUP 1) OR NOT GROUP 2). Median values and one standard deviation, or numbers and percentage are tabulated where appropriate. Statistical comparison was by x^2 or t tests. (N.S. = no significant difference).

		GROUP 1 (REPORTED)		GROUP 2 (NOT REPORTED)		
1.	Number	190		178		
2.	Maternal Age (yrs)	24.9	(SD 4.3)	25.2	(SD 4.5)	N.S.
3.	Maternal Height (cms)	160.5	(SD 5.9)	160.2	(SD 5.8)	N.S.
4.	Maternal Weight (34-36 wks) (kg)	68.5	(SD 9.0)	68.9	(SD 9.0)	N.S.
5.	Social Class I	13	(7%)	18	(10%)	N.S.
	II	54	(29%)	41	(23%)	
	III	61	(32%)	68	(38%)	
	IV	34	(18%)	34	(19%)	
	V	26	(14%)	17	(10%)	
6.	Race White	180	(95%)	174	(98%)	N.S.
	Other	10	(5%)	4	(2%)	
7.	Smoking None	144	(76%)	123	(70%)	N.S.
	< 10/Day	18	(10%)	15	(9%)	
	10 - 20/Day	23	(12%)	25	(14%)	
	> 20/Day	5	(3%)	14	(8%)	
8.	Blood Group 0	98	(52%)	101	(57%)	N.S.
	A	67	(36%)	51	(29%)	
	B	19	(10%)	17	(10%)	
	AB	4	(2%)	8	(4%)	
9.	Consultant 1	30	(16%)	43	(24%)	N.S.
	2	27	(14%)	24	(14%)	
	3	40	(21%)	35	(20%)	
	4	35	(18%)	38	(21%)	
	5	35	(18%)	19	(10%)	
	6	23	(12%)	19	(10%)	
10.	Gestational Age 1st-stage ultrasound (wks)	14.3	(SD 3.2)	14.0	(SD 3.0)	N.S.
11.	Serum Alpha-feto protein: Normal	167		145		N.S.
	High	1		1		
12.	2nd Trimester Amniocentesis	4	(2%)	3	(2%)	N.S.
13.	Gestational Age 2nd-stage ultrasound (days)	247.2	(SD 5.4)	246	(SD 5.8)	N.S.
14.	Presentation 2nd-stage ultrasound Cephalic	184	(97%)	163	(92%)	$P < 0.05$
	Other	6	(3%)	15	(8%)	

TABLE 4 - 3

FINDINGS AT SECOND-STAGE ULTRASOUND EXAMINATION

	GROUP 1 (REPORTED)	GROUP 2 (NOT REPORTED)	
Number	433	444	
Gestational Age (days)	247.1 (SD 5.4)	246.8 (SD 5.6)	N.S.
CRL x TA (cm^3)	1945 (SD 283)	1921 (SD 299)	N.S.
Presentation : Cephalic	411 (95%)	415 (93%)	N.S.
Other	24 (5%)	29 (7%)	
Unsuspected Breech	6	3	
Unsuspected Placenta Praevia	1	0	
Unsuspected Fetal Abnormality	0	1	

suspicion was not reported to the clinical staff. Less major congenital anomalies among the other babies were single cases of cleft palate (Group 1), pyloric stenosis, congenital adrenal hyperplasia and congenital dislocation of hips (Group 2). All malformed babies were of normal birthweight.

CRL X TA values on or below the 10th percentile were classified as abnormal. In a few cases in Group 1 when the CRL X TA value was found to be abnormal, measurement was repeated one week later and again reported to the clinical staff. These latter measurements were not included in calculation of sensitivity and specificity, but are described later.

RESULTS

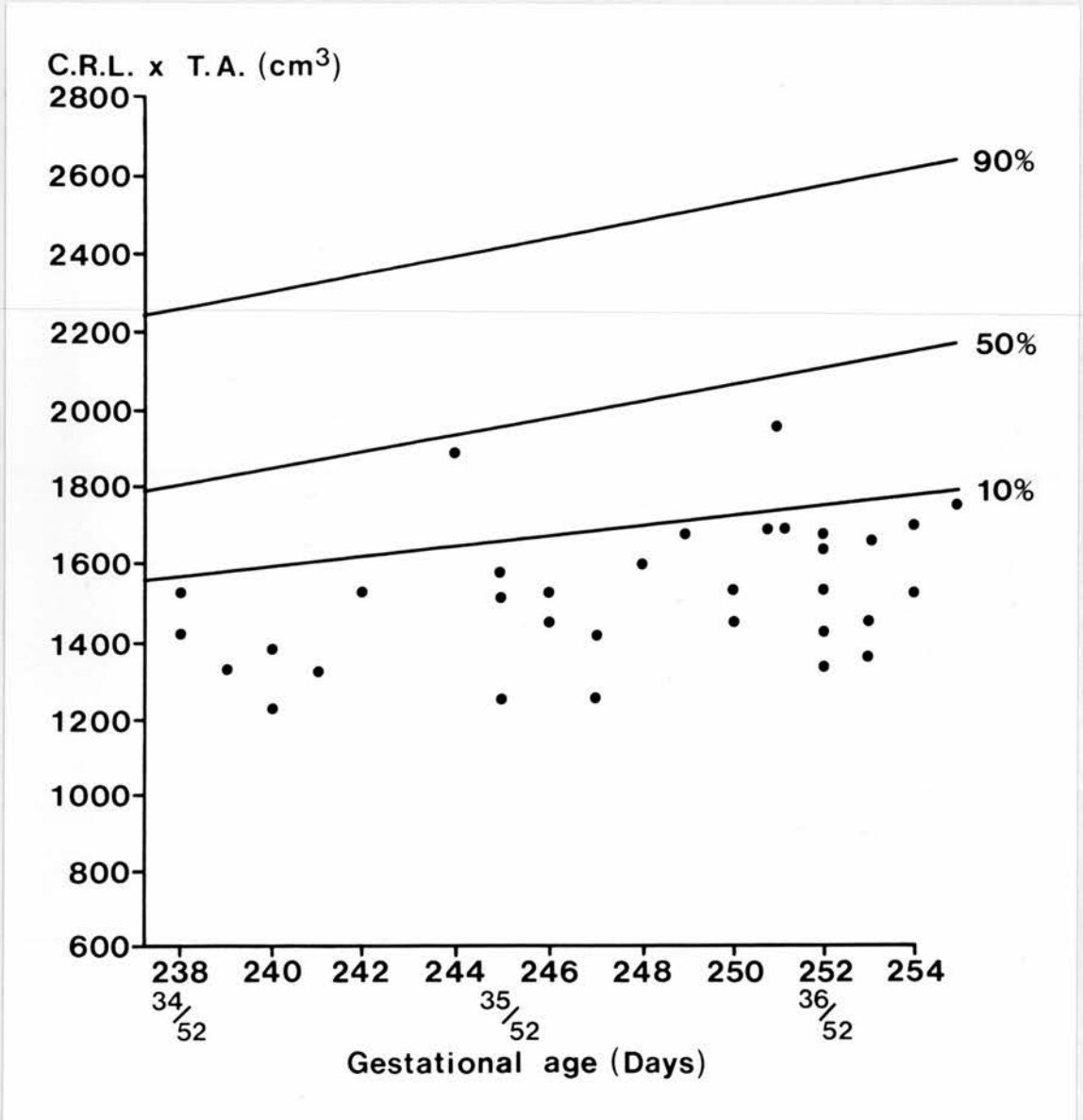
The results of the study will be discussed in two parts: the accuracy of CRL X TA measurement in detecting small-for-dates fetuses, and the impact on fetal outcome and obstetric management of instituting CRL X TA measurement as a screening procedure in low-risk pregnancies.

1. Efficacy of CRL X TA measurement

Of the 33 babies which were small-for-dates at birth, 31 (94%) had CRL X TA values below the demarcation line (Figure 4 - 1) resulting in a false-negative rate of 6%. The remaining 844 babies were of normal birthweight, and of these, 763 (90%) had normal CRL X TA values. The birthweight distribution of the false-positive cases is shown in Table 4 - 4; 21% had birthweights between the 5th and 10th percentiles. Overall the results of CRL X TA measurement in this study may be summarised as follows: sensitivity 94%, specificity 90% and predictive value 28%. There was no significant difference in sensitivity, specificity and predictive value between Groups 1 and 2 (Table 4 - 5).

Fourteen of the subjects in Group 1 who had abnormal CRL X TA values underwent repeat measurement one week later and within the screening period. The second CRL X TA value was normal in 10

Figure 4 - 1



Product of crown-rump length and trunk area : measurements obtained from fetuses that were small-for-dates at birth plotted against gestational age at the time of measurement. The 10th percentile curve is used as the demarcation line.

TABLE 4 - 4

DISTRIBUTION OF BIRTHWEIGHT AND PREDICTION OF OUTCOME BY CRL x TA MEASUREMENT (BOTH GROUPS).

BIRTHWEIGHT	N	TRUE NEGATIVE	FALSE POSITIVE	TRUE POSITIVE	FALSE NEGATIVE
5%	33			31	2
5 - 10%	29	12	17		
10 - 25%	128	94	34		
25 - 50%	203	181	22		
50 - 75%	256	248	8		
75 - 90%	153	153	0		
90 - 95%	41	41	0		
95%	34	34	0		
	877	763	81	31	2

TABLE 4 - 5

PREDICTION OF OUTCOME BY CRL x TA MEASUREMENT

	GROUP 1 (REPORTED)	GROUP 2 (NOT REPORTED)
SENSITIVITY	94%	94%
SPECIFICITY	92%	89%
PREDICTIVE VALUE	31%	24%

Sensitivity is the percentage of small-for-dates babies with abnormal CRL X TA values; specificity the percentage of normal birthweight babies with normal CRL X TA values; predictive value the percentage of babies with abnormal CRL X TA values that were small-for-dates at birth.

cases and the babies were all of normal birthweight; in four cases repeat CRL X TA was again abnormal and three of these babies were small-for-dates at birth. This suggests that the false-positive rate may be reduced by repeat measurement.

The results of CRL X TA measurement were compared with those of crown-rump length alone and of trunk area alone (Table 4 - 6).

2. Impact of CRL X TA measurement on outcome

Fetal outcome was assessed by recording perinatal death, birthweight and Apgar Scores. Also recorded were aspects of obstetric management which could have been influenced in either a positive or negative fashion by the screening programme; these included hospitalisation, rate of induction of labour, mode of delivery and gestational age at delivery. To assess the effects of CRL X TA measurement on outcome, all patients in Groups 1 and 2 were compared (Table 4 - 7) nulliparas in both groups were compared separately (Table 4 - 8), and both small-for-dates subgroups were compared (Table 4 - 9). Statistical analysis, as before, used x^2 of t tests.

DISCUSSION

The hazards of fetal growth retardation make attractive a technique for screening for the small-for-dates fetus. The sensitivity of 94% and specificity of 90% found in this prospective study confirm that CRL X TA measurement is highly effective in detecting the small-for-dates fetus. Alternative strategies and techniques designed to aid detection of the small-for-dates fetus have been described in Chapter 1, and CRL X TA measurement is much more effective than these. Comparison with published reports of the value of alternative ultrasound techniques poses difficulties because there are differences in the definition of small-for-dates, in the selection of the populations studied, in the timing of ultrasound examination and in deciding on a demarcation line which provides the best pay-off between sensitivity and specificity. However, comparison with the results of those of the studies described in Chapter 2 which were large, prospective and of sound methodology,

TABLE 4 - 6

COMPARISON OF PRODUCT OF CROWN-RUMP LENGTH AND TRUNK AREA (CRL X TA). CROWN-RUMP LENGTH (CRL), AND TRUNK AREA (TA) IN DETECTION OF SMALL-FOR-DATES (SFD) FETUSES.

PARAMETER	RATES (%)			
	Sensitivity	False-negative	Specificity	Fale-positive
CRL	66	33	85	15
TA	79	21	88	12
CRL X TA	94	6	90	10

TABLE 4 - 7

OBSTETRIC MANAGEMENT AND FETAL OUTCOME AFTER SECOND-STAGE ULTRASOUND EXAMINATION: ALL SUBJECTS.

	GROUP 1 (REPORTED)	GROUP 2 (NOT REPORTED)	
Number	433	444	
Antepartum Admission:			
- days	1.0 (SD 0.2)	0.9 (SD 0.2)	N.S.
- number	43 (10%)	46 (10%)	N.S.
- reasons:			
hypertension	32 (74%)	27 (59%)	
antepartum haemorrhage	5 (12%)	2 (4%)	
variable lie	1 (2%)	8 (17%)	
suspected growth retardation	3 (7%)	5 (11%)	
other	2 (5%)	4 (9%)	
Induction of Labour	129 (31%)	129 (29%)	N.S.
- reasons:			
post-term	51	51	N.S.
hypertension	38	37	
suspected growth retardation	12	9	
other	28	32	
Delivery			
- gestational age (weeks)	39.3 (SD 1.2)	39.5 (SD 1.2)	N.S.
- mode:			
spontaneous vertex	259 (60%)	281 (53%)	N.S.
forceps	107 (25%)	101 (23%)	
Vacuum	13 (3%)	5 (1%)	
emergency Caesarean Section	37 (9%)	32 (7%)	
elective Caesarean Section	17 (4%)	24 (5%)	
assisted breech delivery	0	1	
Sex: female	220 (51%)	222 (50%)	N.S.
male	213 (49%)	222 (50%)	
Birthweight (kgs)	3.43 (SD 0.5)	3.42 (SD 0.4)	N.S.
Small-for-dates	17 (4%)	16 (4%)	N.S.
Apgar Score (< 7):			
- one minute	37 (9%)	40 (10%)	N.S.
- five minutes	8 (2%)	5 (1%)	
Stillbirths	0	0	
Neonatal Deaths	0	1	

TABLE 4 - 8

OBSTETRIC MANAGEMENT AND FETAL OUTCOME AFTER SECOND-STAGE ULTRASOUND EXAMINATION: NULLIPAROUS SUBJECTS.

	GROUP 1 (REPORTED)		GROUP 2 (NOT REPORTED)		
Number	190		178		
Antepartum admission					
- days	1.1	(SD 4.0)	1.2	(SD 3.6)	N.S.
- number	25	(13%)	26	(15%)	N.S.
- reasons:					
hypertension	22	(88%)	19	(73%)	
antepartum haemorrhage	1		1		
variable lie	0		0		
suspected growth retardation	1		3		
other	1		3		
Induction of Labour	59	(31%)	60	(34%)	N.S.
- reasons:					
post-term	25	(42%)	23	(38%)	N.S.
hypertension	23	(39%)	26	(43%)	
suspected growth retardation	4	(7%)	4	(7%)	
other	7	(12%)	7	(12%)	
Delivery					
- gestational age (weeks)	39.4	(S.D. 1.3)	39.5	(SD 1.3)	N.S.
- mode:					
spontaneous vertex	75	(40%)	73	(41%)	N.S.
forceps	78	(41%)	71	(40%)	
vacuum	7	(4%)	4	(2%)	
emergency Caesarean Section	25	(13%)	22	(12%)	
elective Caesarean Section	5	(5%)	8	(5%)	
Sex: female	105	(55%)	79	(44%)	$P < 0.05$
male	85	(45%)	99	(56%)	
Birthweight (ks)	3.39	(SD 0.47)	3.35	(SD 0.44)	N.S.
Small-for-dates	9	(5%)	7	(4%)	N.S.
Apgar Score (<7):					
- one minute	17	(9%)	20	(11%)	N.S.
- five minutes	3	(2%)	3	(2%)	N.S.
Stillbirths	0		0		
Neonatal Deaths	0		1		

TABLE 4 - 9

OBSTETRIC MANAGEMENT AND FETAL OUTCOME AFTER SECOND-STAGE ULTRASOUND EXAMINATION: BABIES SMALL-FOR-DATES AT BIRTH.

	GROUP 1 (REPORTED)		GROUP 2 (NOT REPORTED)		
Number	17		16		
Antepartum admission					
- days	3.1	(SD 1.7)	1.8	(SD 0.8)	N.S.*
- number	4	(24%)	4	(25%)	N.S.
- reason:					
hypertension	2		1		
suspected growth retardation	2		3		
Induction of labour	4	(24%)	7	(44%)	N.S.
Birthweight (kg)	2.43	(SD 0.2)	2.45	(SD 0.2)	N.S.
Delivery					
- gestational age (weeks)	38.8	(SD 1.1)	39.5	(SD 1.5)	N.S.
- mode:					
spontaneous vertex delivery	11	(65%)	8	(50%)	N.S.
operative delivery	6	(35%)	8	(50%)	
Apgar Score (< 7):					
- one minutes	2		4		
- five minutes	0		0		
Stillbirths	0		0		
Neonatal deaths	0		0		

* As there was a significant difference in the variance of the samples, a separate variance estimate was used in the calculation of the t value (see SPSS Manual).

shows improved detection of small-for-dates fetuses by CRL X TA measurement. The results of this study also confirm the value of measuring CRL in addition to TA.

What, however, of the value of CRL X TA measurement in improving fetal outcome or rationalising obstetric management in low risk patients? This study was carried out between May 1979 and January 1981. During the three years 1979 - 1981 there were 113 perinatal deaths in the Queen Mother's Hospital, grouped in Table 4 - 10 according to local "Yorkhill Classification" (Whitfield : personal communication) and, as can be seen, there were six deaths attributable to fetal growth retardation in the absence of other complications and of fetal deformity; only three of the deaths occurred after 34 weeks. If there were to be any improvement in perinatal mortality among small-for-dates fetuses as a result of CRL X TA measurement in low risk patients it would require, to demonstrate it, the study of many thousands of patients. CRL X TA measurement would be unlikely to have an impact on other causes of perinatal death other than, perhaps, a greater anticipation of the rare cases of shoulder dystocia in fetuses with particularly large measurements.

Improvements that might have been observed within the scope of this study would have been more subtle. Thus improved management of the small-for-dates fetus might have resulted, with a greater use of fetal monitoring and planned delivery leading to a decreased need for operative delivery and to improved condition at birth. The reassurance that a CRL X TA value was normal might have resulted in decreased rates of induction of labour from 40 weeks.

The two groups (reported and non-reported) were well matched. The one statistically significant difference, that of social class distribution, is unlikely to be important. The undoubted relationship between social class and perinatal mortality rate and incidence of fetal growth retardation probably operates through such factors as late attendance at antenatal clinics, poor nutrition as evidenced by maternal height and weight, smoking and high parity. Comparison of these factors and also of the incidence of small-for-dates babies in both groups showed

TABLE 4 - 10

PERINATAL DEATHS IN THE QUEEN MOTHER'S HOSPITAL DURING THE YEARS 1979, 1980, 1981*

CAUSE	N
Fetal deformity	37
Prematurity	20
Unexplained intrauterine death	14
Hypertension	10
Antepartum Haemorrhage	8
Fetal Growth Retardation	6
Intrapartum Asphyxia	5
Trauma	4
Haemolytic Disease	3
Infection	3
Maternal Disease	2
Other	1
	113

Total Births 10,006.

Perinatal Mortality Rate 11.3/1000

*(Whitfield 1983 : personal communication).

no difference. There was, likewise, no difference in outcome (Table 4 - 7). Rates of induction of labour were similar (and high in keeping with the hospital induction rate at the time) as were mode of delivery and the Apgar Scoring and birthweight was the same. There was a similar lack of **effect** in nulliparous sub-**groups** (Table 4 - 8).

The condition of the small-for-dates infants at birth was, in general, good. None required resuscitation at birth and none encountered major neonatal problems. Five of the 16 small-for-dates fetuses in the non-reported group were identified as such by abdominal palpation after second-stage ultrasound examination but prior to delivery. There was no difference in outcome between the two small-for-dates groups. (Table 4 - 9).

To summarise the findings, there was no evidence that screening low risk patients by CRL X TA measurement resulted in any advantage or disadvantage as assessed by evaluation of fetal outcome or obstetric management. The ultrasound examination of almost 900 patients took up considerable machine and operator time and if no improvement could be demonstrated with this size of sample it may be assumed that a screening programme would not be a cost-effective and practical proposition. On the basis of the findings in this study the two-stage ultrasound examination schedule could not be recommended as a general screening technique.

One of the factors that may have contributed to these negative findings is the exclusion of the most disadvantaged group of women who deliver in the Queen Mother's Hospital (those from Drumchapel). Further, the fact that a study is being carried out in a hospital and particularly one which is, in effect, evaluating missed diagnosis by clinical staff, probably heightens awareness of the problem and improves clinical detection rates. Whilst this is no bad thing, many patients who were referred for CRL X TA measurement (details included in Chapter 5) because of clinical suspicion that the fetus was small-for-dates would probably not otherwise have been investigated and this effect may have diluted the impact of CRL X TA measurement.

CHAPTER 5.

EVALUATION OF THE TWO-STAGE ULTRASOUND EXAMINATION SCHEDULE IN HIGH RISK PREGNANCIES

INTRODUCTION

The preceding chapter has confirmed that CRL X TA measurement is, on prospective study, highly effective in detecting the small-for-dates fetus among low risk pregnancies. CRL X TA measurement may also be useful in the assessment of high risk pregnancies not only because of its apparently high sensitivity but also because it need only be measured on a single occasion during the third trimester. A report is available at once in contrast to serial ultrasound measurements which necessitate a time lapse before the fetal growth retardation becomes apparent; further, for logistic reasons, a single ultrasound examination allows the threshold for referral of patients for ultrasound study to be lowered. The need for this has been highlighted by a recent survey of perinatal deaths in the Mersey region of a format similar to the national confidential inquiries into maternal deaths (Mersey Region Working Party, 1982). This study showed that of 182 perinatal deaths with avoidable factors, 13 were due to a failure to detect small-for-dates fetuses despite associated factors which should have prompted suspicion; in a further 7 cases the fetus was diagnosed correctly as small-for-dates but appropriate action was not then taken.

The study reported in this chapter evaluates prospectively the two-stage ultrasound examination schedule in high risk pregnancies.

PATIENTS AND METHODS

The study group comprised 202 patients with singleton pregnancies, referred for measurement of fetal CRL X TA at between 238 and 255 days because they were thought to be at high risk of producing small-for-dates infants. All patients had undergone first-stage ultrasound examination to establish gestational age before 24 weeks (mean 14.4 weeks). Sixty-six (33%) were nulliparous. The main indications for referral for second-stage ultrasound study during the third trimester are shown in Table 5 - 1; by far the commonest indication was the clinical suspicion that the fetus was small-for-dates (127 pregnancies, or 63%). The second-stage examinations were carried

TABLE 5 - 1

MAIN INDICATION FOR REFERRAL FOR ULTRASOUND STUDY, AND OUTCOME.

INDICATION	NO.	BIRTHWEIGHT	
		SFD	Normal
Clinically small-for-dates	127	46	81
Previous small-for-dates	28	4	24
Hypertension	21	3	18
Previous unexplained stillbirth	10	0	10
Decreased fetal movement	3	0	3
Antepartum haemorrhage	3	0	3
Diabetes	3	0	3
Miscellaneous	7	0	7
	202	53	149

(SFD = small-for-dates)

out using the technique described in Chapter 3. Measurement of both CRL and TA were completed successfully in all cases.

Delivery was by elective Caesarean section in 28 pregnancies (14%), and among the remaining 174 labour was induced in 65 cases (37%). Fifty-three infants (26%) had birthweights on or below the 5th percentile (Thomson et al., 1968) and these were classified as small-for-dates. This group had a mean birthweight of 2.23 kg (range 1,52 - 2,77 kg) and mean gestational age at delivery of 37,7 weeks. The distribution of birthweight among all the babies is shown in Figure 5 - 1; 149 (74%) had birthweights less than the 25th percentile.

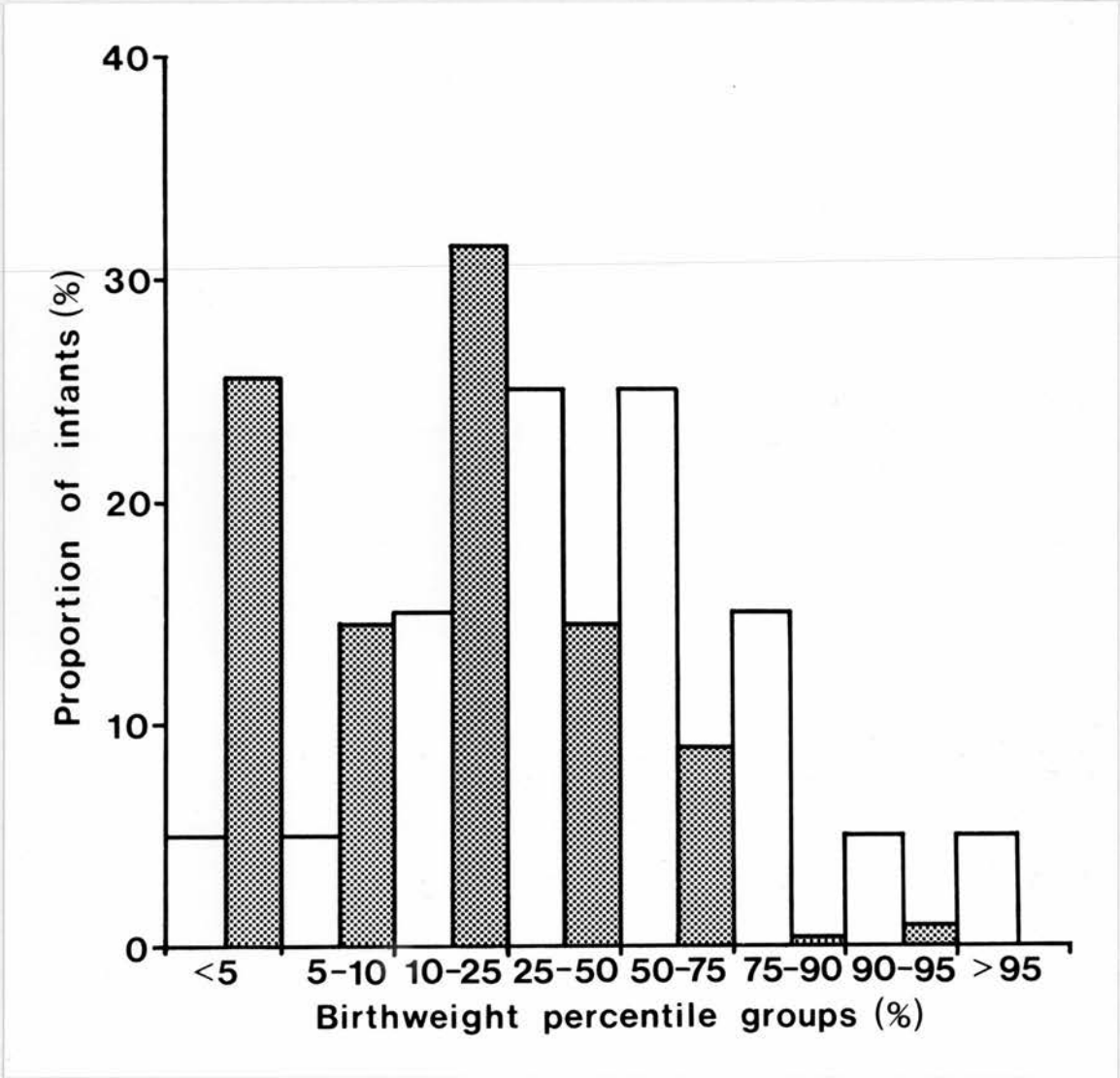
There was one perinatal death. The infant, a macerated stillbirth weighing 2,29 kg and delivered at 35 weeks, had a birthweight greater than the 5th percentile but less than the 10th and was therefore classified as of normal birthweight; the cause of death remained unexplained after pathological examination.

RESULTS

The results of CRL X TA measurement are shown in Figure 5 - 2 and Table 5 - 2. Of the 53 fetuses that were small-for-dates at birth, 49 (92%) had CRL X TA results below the demarcation line. The false-negative rate was therefore 8% (percentage of small-for-dates infants with normal CRL X TA value). The false-positive rate was 42% (percentage of normal infants with low CRL X TA values), 35% of the infants in this category having birthweights greater than the 5th but less than the 10th percentile.

Using identical criteria, the results of measurement of CRL alone and of TA alone were compared with those of CRL X TA and the results are shown in Table 5 - 3. The 91% detection rate by measurement of TA represented a failure to predict only 5 of the 53 fetuses that were eventually small-for-dates at birth (Figure 5 - 3), and was similar to the rate achieved by CRL X TA measurement. CRL alone was less effective but associated with a lower false-positive rate.

Figure 5 - 1



Histogram showing the birthweight distribution of study babies (shaded columns) contrasted with that expected from the Aberdeen data (plain columns).

TABLE 5 - 2

RESULTS OF CROWN-RUMP LENGTH X TRUNK AREA (CRL X TA) MEASUREMENT AND DETECTION OF SMALL-FOR-DATES (SFD) FETUSES.

Prediction by CRL X TA	No.	Birthweight	
		SFD	Normal
SFD	111	49	62
Normal	91	4	87
	202	53	149

TABLE 5 - 3

COMPARISON OF CRL, TA AND CRL X TA IN DETECTION OF THE SMALL-FOR-DATES (SFD) FETUS.

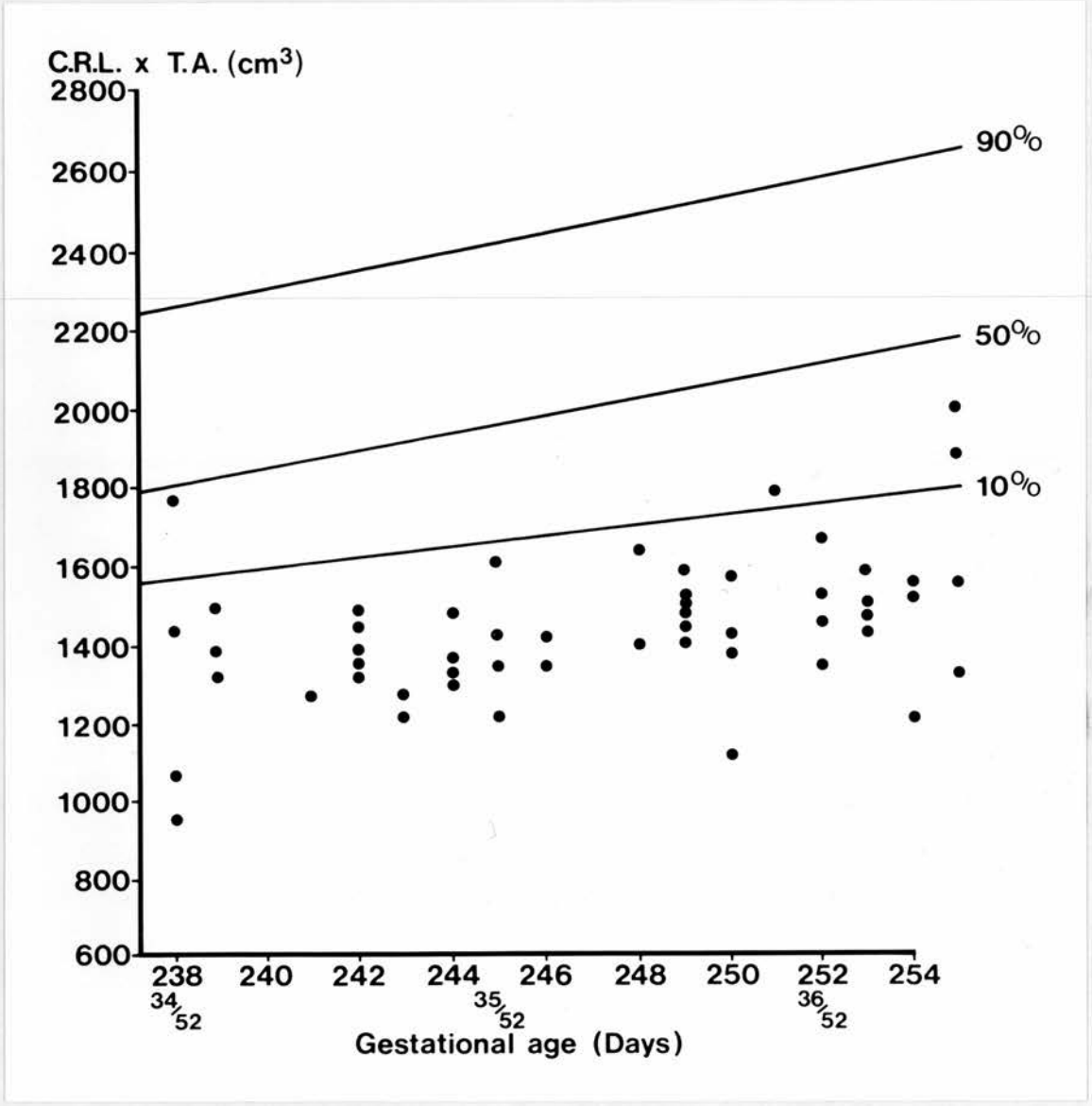
Parameter	Rates (%)		
	SFD detected	False-negative	Fale-positive
CRL	64	36	27
TA	91	9	38
CRL X TA	92	8	42

TABLE 5 - 4

RESULTS OF CROWN-RUMP LENGTH X TRUNK AREA (CRL X TA) MEASUREMENT AND DETECTION OF SMALL-FOR-DATES (SFD) FETUSES AMONGST PATIENTS THOUGHT CLINICALLY TO HAVE AN SFD FETUS.

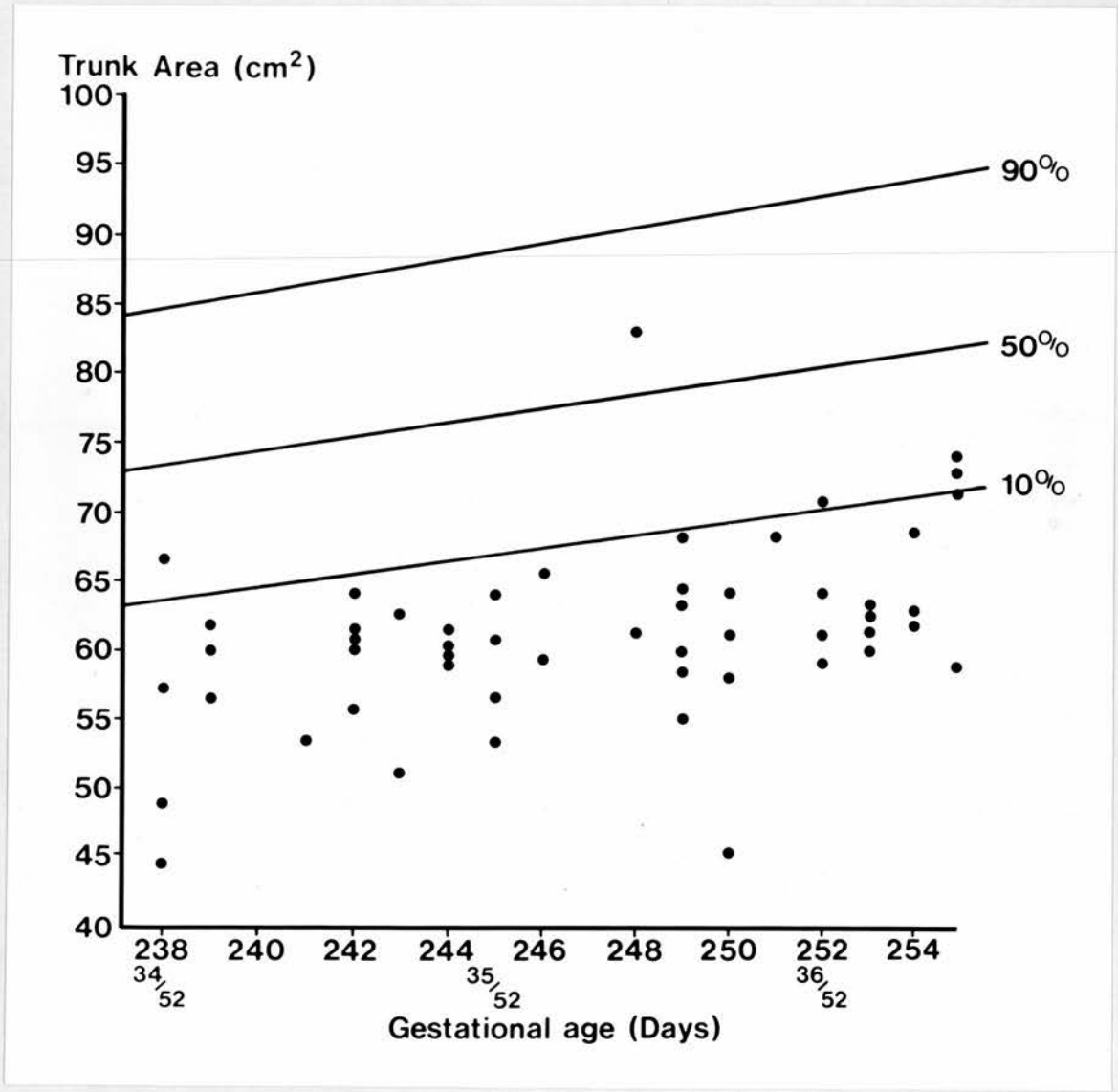
Prediction by CRL X TA	No.	Birthweight	
		SFD	Normal
SFD	87	43	44
Normal	40	3	37
	127	46	81

Figure 5 - 2



Product of crown-rump length and trunk area (CRL X TA) : measurements obtained from those fetuses that were small-for-dates at birth, plotted against gestational age at the time of measurement.

Figure 5 - 3



Trunk area measurements obtained from those fetuses that were small-for-dates at birth, plotted against gestational age at the time of measurement.

Considering only the 127 fetuses suspected clinically to be small-for-dates 46 (36%) were actually small-for-dates at birth and 43 of these (93%) were identified correctly by CRL X TA measurement, with 7% false-negative and 54% false-positive rates. (Table 5 - 4).

DISCUSSION

This prospective study confirms the high sensitivity of CRL X TA measurement, 49 out of 53 small-for-dates fetuses (92%) being correctly identified. Whilst the false-negative rate of 8% is similar to that in the studies reported in Chapters 3 (6%) and 4 (6%), the false-positive rate is much higher, 42% compared with 12% and 10%; this can be attributed to the skewed birthweight distribution of the high risk babies studied, threequarters of whom had birthweights below the 25th percentile. As discussed earlier the demarcation line for CRL X TA measurement was chosen to minimise false-negative results whilst accepting a significant false-positive rate, which should not pose a clinical problem if CRL X TA values are interpreted appropriately. The results presented here indicate a 44% chance that the fetus with a CRL X TA value below the demarcation line will be small-for-dates at delivery, and this calls for further assessment rather than immediate intervention. Thus, the timing and mode of delivery should be based on such factors as past obstetric history, current pregnancy complications, the state of fetal lung maturation, the ripeness of the cervix, biochemical assessment, further ultrasound evaluations for fetal measurement and assessment of amniotic fluid volume and, perhaps most importantly, cardiotocographic findings (Flynn et al., 1979; McCune et al., 1983). Many healthy small-for-dates fetuses and appropriately-grown "false-positives" may be managed conservatively in this way.

Despite the high false-positive rate, CRL X TA measurement was useful in the management of these high risk pregnancies; it not only sometimes confirmed a clinical suspicion that the fetus seemed small-for-dates and successfully picked out almost all (92%) of the fetuses eventually small-for-dates at birth, but it also "corrected" half of the clinical false-positives (Table 5 - 4) because a normal

CRL X TA value virtually excludes the possibility of the fetus being small-for-dates. Since CRL X TA measurement need be carried out once only, and because it is both very quick and simple to perform, the threshold for referral of patients for ultrasound study may be lowered.

In contrast to the findings reported in Chapters 3 and 4, this study showed no advantage for measuring CRL X TA compared with TA alone. The explanation for this difference is uncertain.

CHAPTER 6.

EVALUATION OF THE TWO-STAGE ULTRASOUND EXAMINATION SCHEDULE IN TWIN PREGNANCIES.

INTRODUCTION

The perinatal mortality rate from twin pregnancies is high. In Scotland, in 1977, it was 95 per 1000, six times greater than that from singleton pregnancies (McIlwaine et al., 1979b). While preterm delivery remains the major cause of perinatal death, fetal growth retardation is also important (Farr, 1975; Manlan and Scott, 1978; McIlwaine et al., 1979b; Desgranges et al., 1982). The effective antenatal detection of the small-for-dates twin fetus would therefore be an important advance.

As discussed earlier, abdominal palpation is of limited value in identifying even the small-for-dates singleton fetus; in twin pregnancies there are obviously greater difficulties in assessing the size of either fetus in the presence of the other, and such assessment may be further complicated by polyhydramnios. Biochemical assessment is also unsatisfactory. Maternal urinary oestriol excretion reflects the combined function of both feto-placental units together and is an inaccuracte index of fetal jeopardy and of fetal growth retardation in twin pregnancies (Duff and Brown, 1974; Duncan et al., 1979). Indeed, oestriol values may continue to rise after the intrauterine death of one of the twins (Duff and Brown, 1974). Plasma HPL levels may be within normal limits, even for twin pregnancies, despite fetal growth retardation and poor fetal outcome (Duncan et al., 1979).

In contrast, diagnostic ultrasound allows the separate assessment of each twin fetus. It is surprising that, despite the large literature on ultrasonic detection of fetal growth retardation in singleton pregnancies, little has been published on its value in twin pregnancies. Reports have usually been anecdotal (Dorros, 1975; Weinstein and Spirt, 1979) or have concentrated on the difference between biparietal diameter measurements of each fetus in individual twin pregnancies (Houlton 1977; Haney et al., 1978; Houlton et al., 1981). Since fetal growth retardation may affect one or both of twins, use of the other twin as a standard to assess growth or size is illogical and misleading. One study (Divers and Hemsell, 1979) did compare BPD growth of twins with normal singleton values and there were false-negative rates of more

than 50% in the detection of small-for-dates twin fetuses, but the series was small and the discussion of methodology inadequate.

The author (Neilson, 1981) assessed retrospectively the results of serial biparietal cephalometry in twin pregnancies during the years 1975 to 1979 in the Queen Mother's Hospital. Sixty-six pregnancies which fulfilled the following criteria were selected for study: certain menstrual data and/or early ultrasound assessment of gestational age, at least two ultrasound examinations after the 28th week with the last examination occurring within three weeks of delivery (in 89% the last examination was within two weeks). There was a total of 321 ultrasound examinations (642 individual attempts at BPD measurement), a mean of 4.9 examinations per patient. BPD values were plotted on the chart of Campbell and Newman (1971) which was derived from the measurement of singleton fetuses. The greater BPD value at each examination was assumed to relate to the same twin, and to represent the twin of greater birthweight. Both "late flattening" and "low growth profile" BPD patterns (Campbell 1974b) were classified as abnormal. In 82 individual attempts at measurement (13%) no BPD value was obtainable. Analysis of the results of the study showed that only 24 (56%) of the 36 small-for-dates infants had shown abnormal BPD growth; in addition only 51% of fetuses which did show abnormal BPD growth were, in fact, small-for-dates at delivery. Twelve (9%) of the 132 curves could not be interpreted. It was concluded that serial biparietal cephalometry is not effective in detection of the small-for-dates twin fetus.

This chapter describes an evaluation of the use of CRL X TA measurement in twin pregnancies.

PATIENTS AND METHODS

Thirty-one patients with twin pregnancies were studied prospectively. All had had ultrasound assessment of gestational age (and ultrasound diagnosis of twin pregnancy) before 20 weeks. All underwent the second-stage examination at between 34 and 36 weeks for the measurement of CRL and TA of both fetuses by the technique described in Chapter 3.

In all cases both fetuses were measured. A single assumption was made in analysis : that the greater CRL X TA value related to the twin of greater birthweight.

Two babies were stillborn, both from the same pregnancy; both deaths were attributed to utero-placental insufficiency. There were no other perinatal deaths and no malformed fetuses.

RESULTS

Nineteen of the 62 babies were small-for-dates at delivery; all (including both stillborn small-for-dates fetuses) had CRL X TA values below the demarcation line (Figure 6 - 1). Of the 43 babies of normal birthweight, 32 had results above the demarcation line. Since the assumption that the greater CRL X TA value represented the twin of greater birthweight may not always be valid, the predictive value of pairs of CRL X TA results was assessed (Table 6 - 1). Of the 12 pregnancies in which both CRL X TA values were below the demarcation line, 11 produced infants of which one (5 cases) or both (6 cases) were small-for-dates. When both CRL X TA values were above the 10th percentile (13 cases), all babies were of normal birthweight.

TABLE 6 - 1

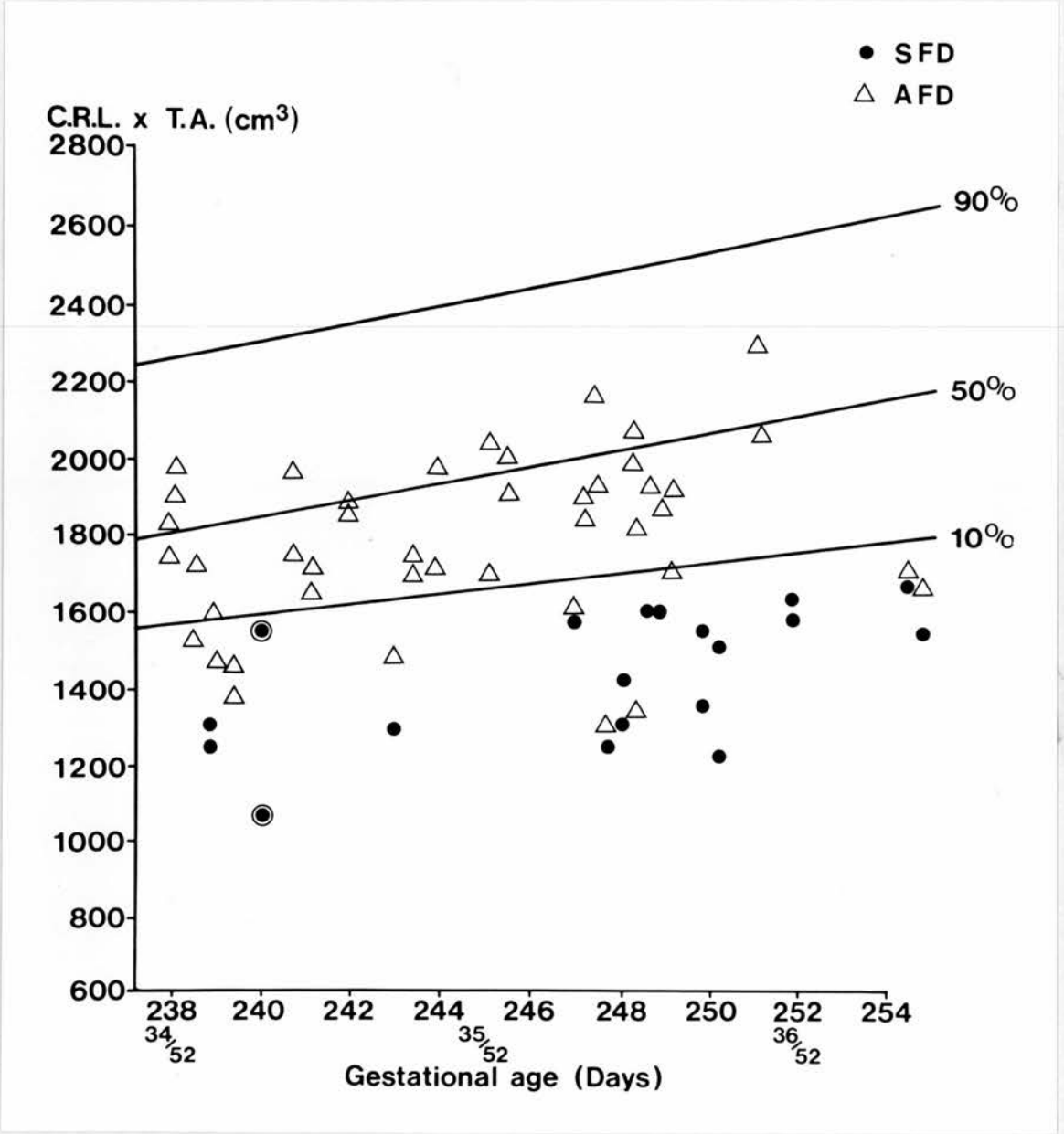
Product of crown-rump length and trunk area (CRL X TA) and prediction of outcome by paired values. (SFD = small-for-dates)

CRL X TA		N	Both SFD	SFD + Normal	Both Normal
Both	10%	12	6	5	1
10%	10%	6	0	2	4
Both	10%	13	0	0	13

DISCUSSION

The mean birthweight of twins is lower than that of a singletons and some authors have therefore recommended that specific birthweight standards for twins should be used (Schneider et al., 1978; Leveno et al., 1979). This is illogical. Fetal growth is determined by an interaction between intrinsic growth potential and environmental factors

Figure 6 - 1



Product of crown-rump length and trunk area (CRL X TA) : measurements obtained from twin fetuses, plotted against gestational age at the time of measurement. The triangles represent fetuses of normal birthweight; the dots represent those that were small-for-dates at birth. (The encircled dots represent the stillborn fetuses).

and it is known, as has been discussed earlier, that those singleton fetuses whose growth is retarded by a failure of environmental support are at high risk of perinatal death and damage. Since there is no evidence that twins have a lesser intrinsic growth potential than singletons, their smaller average size must be attributed to an environmental effect. This is substantiated by both birthweight (McKeown and Record, 1952; Naeye et al., 1966; Bleker et al., 1979) and ultrasound (Bleker et al., 1977) studies. Consequently, when assessing perinatal risks, singleton standards should be used to define abnormalities of fetal size, growth and birthweight in twins, as has been done in this study.

The data presented here show that CRL X TA measurement is also highly effective in detecting the small-for-dates twin fetus, identifying all 19 such fetuses in this study. Whilst comparison between retrospective and prospective studies must be approached with caution, these results indicate several advantages in using the CRL X TA index, compared with serial cephalometry, in twin pregnancies which reach at least 34 weeks. It need be measured only once, and it seems to be measurable in each fetus in every case. Interpretation is easy, it is much more effective in detecting the small-for-dates twin, and it is associated with a lower false-positive rate.

CHAPTER 7

PREDICTION OF THE LARGE-FOR-DATES FETUS BY CRL X TA MEASUREMENT

INTRODUCTION

Perinatal mortality rate is increased at both extremes of the birthweight range. According to Ounsted and Ounsted (1973) small-for-dates fetuses have a mortality rate six times and large-for-dates fetuses double that of babies of "optimum birthweight". In the absence of impaired glucose tolerance in the mother, the particular risks that face the very large baby are those that relate to its size - cephalopelvic disproportion, difficult vaginal delivery and shoulder dystocia (Gollin et al., 1958; Bolton, 1959; McEwan and Murdoch, 1966; Ounsted, 1969). Antenatal identification by ultrasound that a fetus is large-for-dates may be of some value in indicating the need for particularly careful supervision during labour with caution if progress ceases during either the first or second stages of labour. This information may also be of value in management after previous Caesarean section, when the fetus presents by the breech and when the mother is diabetic. In the opinion of the author the theoretical advantages of induction of labour at 40 weeks when the fetus is particularly large are outweighed by the disadvantages of less efficient uterine action in induced rather than spontaneous labour, but this is perhaps open to question. What is clear, however, is that antenatal detection of the large-for-dates fetus is of less clinical importance than detection of the small-for-dates fetus.

In this chapter, data obtained from the studies reported in this thesis have been analysed to assess the efficacy of CRL X TA measurement in predicting those babies which were found to be large-for-dates at birth. Large-for-dates has been defined as birthweight equal to or greater than the 95th percentile (Thomson et al., 1968).

RESULTS

From the studies reported in Chapters 3 and 4, 54 large-for-dates babies were identified (there were none in the high risk and twin groups reported in Chapters 5 and 6). The CRL X TA values of the large-for-dates babies are shown in Figure 7 - 1, 26 (48%) having

results above the demarcation line (90% percentile), 22 (41%) between the mean and 90th percentile, and 6 (11%) below the mean. The false-positive rate calculated from the data of the 877 women included in the controlled trial (Chapter 4) was 2.1%; of these 19 babies with CRL X TA values above the demarcation line but which were not large-for-dates at birth, nine had birthweights between 90th and 95th percentiles and all but one had birthweights above the mean. The outcome of the large-for-dates babies in the controlled trial are shown in Table 7 - 1.

TABLE 7 - 1

OUTCOME OF LARGE-FOR-DATES BABIES IN THE CONTROLLED TRIAL ACCORDING TO WHETHER THE CRL X TA VALUE HAD BEEN REPORTED OR NOT

	REPORTED	NON-REPORTED	
Number	19	15	
Induction of labour	10	9	N.S.
Mode of delivery:			
Spontaneous vertex	11	9	N.S.
Surgical	8	6	
Apgar Score $<$ 7:			
one minute	1	4	
five minutes	1	2	

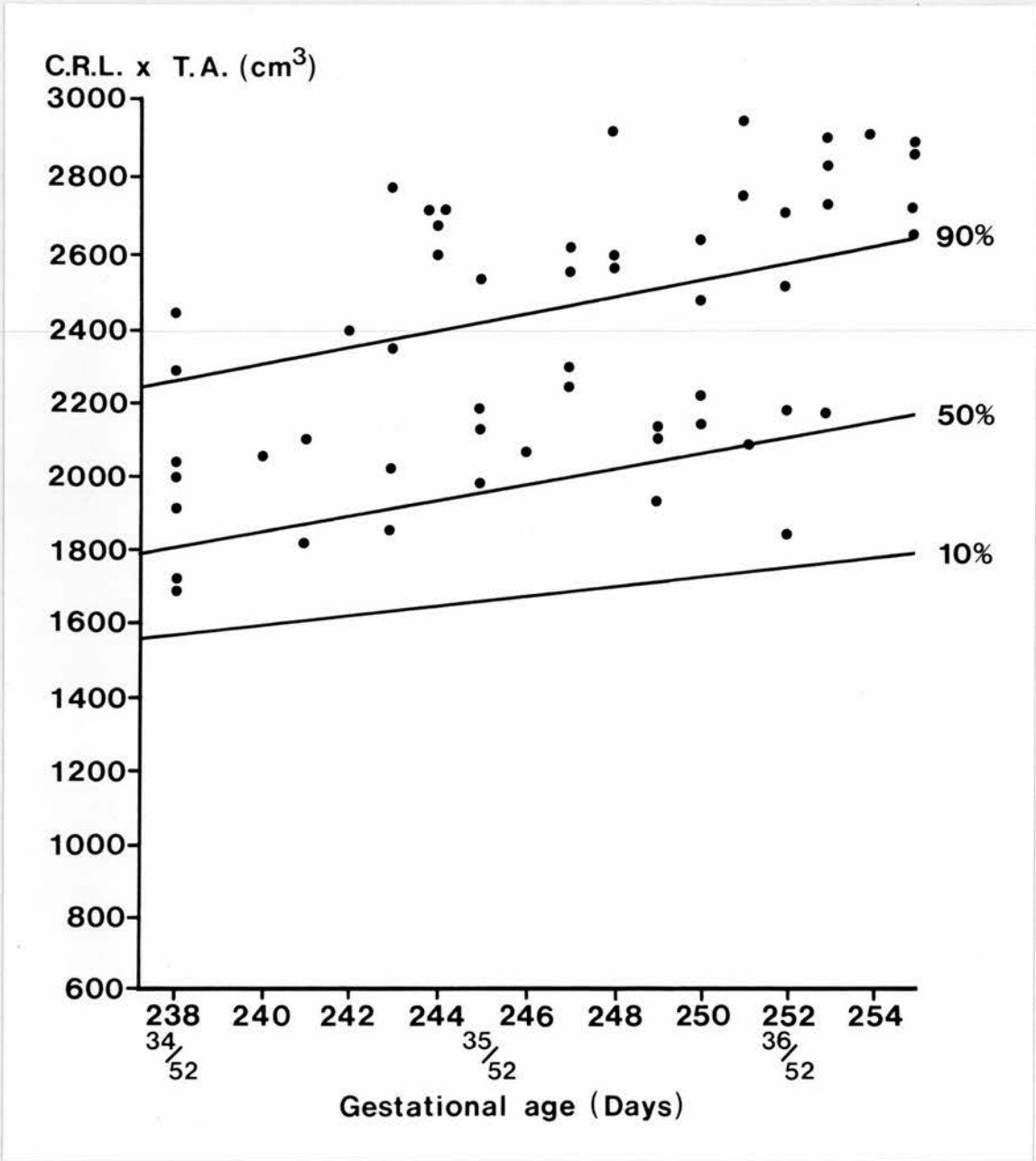
The baby with the low Apgar Score in the reported group appeared dead at birth following shoulder dystocia but was successfully resuscitated and appeared normal at paediatric follow-up. There were no perinatal deaths. The incidence of low Apgar Scores in the non-reported group appears high but the numbers are too small to draw any conclusions.

CONCLUSIONS

Large-for-dates babies show a wide range of CRL X TA values when measured at between 34 and 36 weeks. Using the 90th percentile as the demarcation line, approximately half of the large-for-dates babies

were identified antenatally by CRL X TA measurement, with a negligible false-positive rate. No obvious benefit could be ascertained from the available data.

Figure 7 - 1



Product of crown-rump length and trunk area (CRL X TA) : values obtained from fetuses which were large-for-dates at birth.

CHAPTER 8

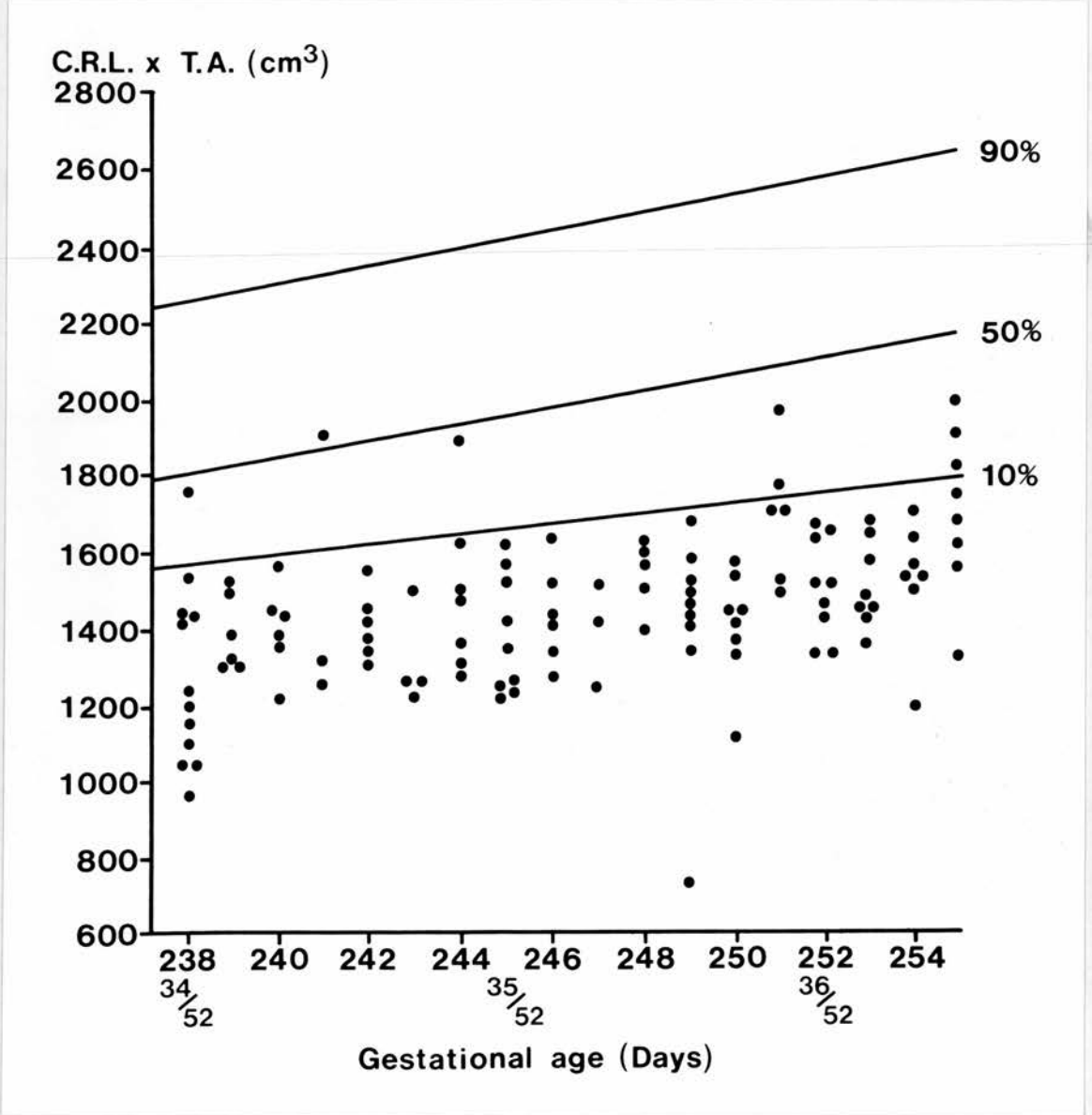
GENERAL CONCLUSIONS

The initial study reported in Chapter 3 indicated that measurement of fetal CRL x TA by ultrasound at between 34 and 36 weeks was highly effective in detecting the small-for-dates fetus. Of much greater importance than the assessment of reproducibility of these measurements was the evaluation of CRL x TA measurement in detecting such fetuses prospectively and the results in both singleton (Chapters 4 and 5) and twin (Chapter 6) pregnancies have confirmed the accuracy of this technique. Pooling the results obtained on the 1553 patients with singleton pregnancies shows that 114, or 93%, of the 122 babies that were small-for-dates at birth had been identified in advance by CRL x TA measurement (Figure 8 - 1). Comparison with the pooled results of measurement of CRL alone and of TA alone is shown in Tables 8 - 1 and 8 - 2. False-positive rates obtained with CRL x TA measurement varied with the nature of the different groups studied, from 12% in a largely unselected population (Chapter 3) and 10% among low risk patients (Chapter 4) to 22% and 42% respectively in the groups with the highest concentrations of small-for-dates babies, namely the twin pregnancies (Chapter 6) and high risk patients (Chapter 5).

CRL x TA had been selected for further study in preference to TA alone (page 76) without, at completion of the initial study, statistical confirmation of improved efficacy. Use of the pooled data does allow statistical evaluation. False-positive predictions were virtually identical for CRL x TA (N = 199) and for TA (N = 206). Of the 122 small-for-dates singleton babies, 103 were correctly predicted by both CRL X TA and TA, eight were not identified by either parameter and 11 were predicted by CRL x TA but not by TA, (no small-for-dates baby was correctly identified by TA, but not by CRL x TA). This suggests that CRL x TA is less likely to produce a false-negative result than TA and this hypothesis has been evaluated by McNemar's Test. The test statistic obtained, 11, provides, by reference to the chi-squared table with one degree of freedom, a p value of less than 0.001. This analysis vindicates the selection of CRL x TA in preference to TA with a less than 0.1 percent possibility that the better sensitivity of CRL x TA is due to chance.

Whilst the results reported in Chapter 4 indicates that CRL x TA measurement cannot be recommended as a general screening procedure, the effectiveness of the technique combined with its simplicity and speed of measurement on only a single occasion means that it may, with advantage, be performed on all patients in whom there is any reason to suspect the possibility of fetal growth retardation. As real-time ultrasound becomes increasingly used in obstetrics (thus excluding, with currently available equipments, the possibility of measurement of CRL in late pregnancy), the by no means unsatisfactory results obtained by measuring TA alone are of considerable relevance. Nevertheless, identification of a practical index of fetal length and flexion, suitable for realtime apparatus, would appear desirable.

Figure 8 - 1



Product of crown-rump length and trunk area (CRL X TA) : pooled values obtained from fetuses that were small-for-dates at birth.

TABLE 8 - 1

POOLED RESULTS FROM SINGLETON PREGNANCIES: COMPARISON OF CRL, TA AND CRL x TA MEASUREMENT

	N	True Positives	False Negatives	N	True Negatives	False Positives
CRL	122	81	41	1431	1211	220
TA	122	103	19	1431	1225	206
CRL x TA	122	114	8	1431	1232	199

TABLE 8 - 2

POOLED RESULTS FROM SINGLETON PREGNANCIES: EFFICACY OF MEASUREMENT

Parameter	Sensitivity	Specificity	Predictive Value Positive Result	Predictive Value Negative Result
CRL	66 %	85 %	27 %	97 %
TA	84 %	86 %	33 %	98 %
CRL x TA	93 %	86 %	36 %	99 %

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