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**DOPPLER STUDIES IN
SMALL FOR GESTATIONAL AGE
PREGNANCIES AND THE INFLUENCE OF
PERINATAL VARIABLES
ON POSTNATAL OUTCOMES**

Lesley Margaret Elizabeth McCOWAN

**A thesis submitted for the degree Doctor of Medicine
University of Auckland
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PUBLICATIONS RESULTING FROM THIS THESIS

Chapter 5

A randomised controlled trial of low dose aspirin to increase birthweight in SGA pregnancies with abnormal umbilical artery Doppler studies. L McCowan, J Harding, A Roberts, S Barker, C Ford, A Stewart. Accepted for publication by British Journal of Obstetrics & Gynaecology 1999.

Chapter 6

A pilot randomised controlled trial of two regimens of fetal surveillance in small for gestational age fetuses with normal umbilical artery Doppler studies. L McCowan, J Harding, A Roberts, S Barker, C Ford, A Stewart. Submitted to American Journal of Obstetrics and Gynecology March 1999.

Chapter 7

Umbilical artery Doppler studies in small for gestational age babies reflect disease severity. L McCowan, J Harding, A Stewart. Submitted to American Journal of Obstetrics & Gynecology December 1998.

Chapter 8

Perinatal predictors of growth at six months in small for gestational age babies. L McCowan, J Harding, S Barker, C Ford. Submitted to Early Human Development March 1999.

Chapter 9

Perinatal predictors of neurodevelopmental outcome in small for gestational age children at 18 months of age. This chapter has not been submitted for publication.

This has been deferred until the whole SGA cohort reaches 18 months of age.

ABBREVIATIONS USED IN THIS THESIS

AC	abdominal circumference
AGA	appropriate for gestational age
BRS	behavioural rating score
BSID	Bayley scales of infant development
D	diastolic
EGF	epidermal growth factor
eNOS	endothelial nitric oxide synthase
ET	endothelin
HC	head circumference
HGH-v	placental variant of human growth hormone
IGF	insulin like growth factor
IGF-BP	insulin like growth factor binding protein
IUGR	intrauterine growth restriction
LSCS	lower segment caesarean section
MDI	mental developmental index
NIDDM	non insulin dependent diabetes
NO	nitric oxide
NOS	nitric oxide synthase
PDI	motor developmental index
RI	resistance index
S	systolic
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
TGF α	transforming growth factor α
UA	umbilical artery

ABSTRACT

Background, hypotheses and aims

Poor fetal growth is associated with increased perinatal morbidity and mortality. Recently the topic of poor fetal growth has generated considerable research interest, as numerous epidemiological studies have demonstrated that small size at birth is also associated with increased risks of adult cardiovascular diseases and non-insulin dependent diabetes. Antenatal treatment aimed at improving fetal growth might therefore reduce perinatal morbidity, as well as later complications of being born small for gestational age (SGA). SGA fetuses with abnormal umbilical artery Doppler studies have placental vascular pathology. Low dose aspirin, which inhibits the production of the powerful vasoconstrictor thromboxane, might therefore increase placental blood flow and fetal growth. The hypothesis in the first antenatal study was that treatment of SGA pregnancies, with abnormal umbilical artery Doppler studies, with aspirin (100 mg) for ≥ 14 days, would increase fetal weight.

As perinatal morbidity and mortality are increased in SGA pregnancies most obstetricians advocate a programme of regular fetal surveillance. Outpatient management with twice weekly fetal surveillance has been usual practice in our hospital in uncomplicated SGA pregnancies. These frequent checks may be unnecessary when umbilical artery Doppler studies are normal as the risk of serious perinatal morbidity is low. More conservative management in SGA pregnancies with normal umbilical artery Doppler studies has been suggested by several authors but has only been evaluated in one previous trial, where hospitalisation was usual practice. In the second antenatal study we therefore wished to test the hypothesis that the frequency of fetal surveillance could be reduced from twice weekly to fortnightly, in SGA pregnancies with normal umbilical artery Doppler studies, without increasing maternal or perinatal morbidity.

Abnormal umbilical artery Doppler studies have been shown in a number of reports to be associated with increased perinatal mortality and morbidity, in SGA pregnancies. Previous investigators have not considered the potential confounding effects of both gestational age at delivery and birthweight in relation to umbilical artery Doppler status. SGA babies with normal umbilical artery Doppler studies,

have a low risk of complications and have been called 'small normal babies' although there is little data to support this claim. In the third antenatal study the following hypotheses were tested: that abnormal umbilical artery Doppler studies would predict newborn morbidity in SGA babies, independent of birthweight and gestational age; that compared with SGA babies with abnormal umbilical artery Doppler studies, SGA babies with normal umbilical artery Doppler studies would have low rates of newborn morbidity and malnutrition; and that their mothers would be smaller, have different ethnic distribution, and have lower rates of vascular problems in pregnancy than mothers of SGA babies with abnormal umbilical artery Doppler studies.

After birth approximately 20% of SGA babies fail to show catchup growth and remain short at two years of age. Persisting short stature has been associated with later psychological difficulties, abnormal neurodevelopmental testing in childhood, poor school performance and hypertension in childhood and adult life. Most catchup growth occurs in the first six months after birth and most children who are small at six months will not show further catchup growth. Early identification of children who will remain small may enable interventions aimed at improving later outcomes. There are no previous reports of the influence of perinatal variables on size at six months. In the first postnatal study in this thesis we therefore chose to investigate the perinatal factors associated with small size at six months of age. We tested the hypotheses that children who were small at six months would: have been diagnosed SGA earlier in pregnancy; be more likely to have abnormal umbilical artery Doppler studies; have smaller body proportions at birth; and be more likely to have normal ponderal indices at birth.

Previous studies, mostly of children born in the 1960s and 1970s, have reported more abnormal neurodevelopmental test results in children who were SGA at birth compared with appropriate weight for gestational age children. There are very few published studies of neurodevelopmental outcome in SGA children born in the 1990s, who have had the advantage of recent advances in antenatal and especially newborn care. The aims of the second postnatal study were therefore to: assess neurodevelopmental outcome in a cohort of SGA children at 18 months and compare results to a reference population; determine whether one or more of the following perinatal variables might be predictive of abnormal neurodevelopmental test results:

early recognition of SGA antenatally, abnormal antenatal Doppler results, lack of participation in the antenatal studies in SGA pregnancies, gestation at delivery, head size at birth, head growth from birth to six months, and ponderal index at birth.

METHODS

All studies were conducted at National Women's Hospital, a tertiary referral centre in New Zealand. Women were recruited to the antenatal studies between March 1993 and July 1997 and the postnatal studies are still ongoing. The studies were approved by the regional ethics committee.

Antenatal Studies

Study 1: The study population comprised pregnant women with singleton fetuses who met the following criteria: SGA on scan (abdominal circumference <10th percentile), scan performed at ≤ 20 weeks and no evidence of fetal abnormality, gestational age at recruitment between 24 and 36 weeks, and two abnormal umbilical artery Doppler studies in the last few days (resistance index >95th percentile). Consenting women with no contraindications to aspirin, were randomly allocated to treatment with aspirin (100 mg) or identical placebo. The main outcome measures were birthweight and other measures of newborn morphometry and morbidity.

Study 2: The study population was the same as in study one, with the exception that participants in this study had normal umbilical artery Doppler studies (resistance index ≤ 95 th percentile). Consenting women were randomly allocated to planned fortnightly or planned twice weekly tests of fetal surveillance. Those in the twice weekly group had twice weekly nonstress tests, biophysical profile scores, umbilical and cerebral Doppler studies. The same tests were performed at fortnightly intervals in the fortnightly group. Both study groups had fortnightly growth scans. The main outcome measures were markers of maternal morbidity (caesarean section, induction of labour) and newborn morbidity (SGA, admission to newborn nursery, duration of hospital stay, acidosis at birth).

Study 3: The study population was those who participated in Study 1 and 2 who delivered small for gestational age babies (birthweight <10th percentile). Pregnancy outcomes were compared in these SGA babies and their mothers in relation to

umbilical artery Doppler status. The main outcome measures were: perinatal morbidity (newborn nursery admission and length of stay, hypoglycemia, acidosis, periventricular haemorrhage) and mortality; newborn morphometry (birth measurements and standard deviations scores); maternal hypertensive disease and morbidity (caesarean section, induction of labour).

Postnatal Studies

The study population was babies from the antenatal studies who were SGA at birth (birthweight <10th percentile) and SGA babies who had not participated in the antenatal studies but met the following criteria: scan at ≤ 20 weeks, SGA in pregnancy, umbilical artery Doppler studies performed in the two weeks preceding delivery and no evidence of chromosomal or congenital abnormality after birth.

Study 4: Measurements of weight, length (or height) and head circumference were performed at 3, 6, 9, 12, 15, 18, 21 and 24 months corrected age after birth by the research midwife. All children recruited to the study (who were not lost to followup) had completed growth checks at six months. They comprise the study population. The aim was to determine the perinatal factors associated with small size at six months. The main outcome measures were shortness (length <10th percentile), underweight (<10th percentile), small head circumference (<10th percentile) and overall smallness (length and weight <10th percentile). Catchup growth was also estimated as the difference in z score measurements (Δ z score) obtained between birth and six months. A negative Δ z score implied failure of catchup growth.

Study 5: SGA babies had neurodevelopment assessed at 18, 36 and 72 months corrected age. The study population comprised those who had completed neurodevelopmental assessment at 18 months corrected age. Neurodevelopment was assessed by a psychologist, using the Bayley Scales of infant development which consists of three components: the mental development index (MDI), motor development index (PDI) and behavioural rating score (BRS). The main outcome measures in this study were abnormal test results in the components of the Bayley scales defined as: an MDI or PDI score >1SD below the mean, or a BRS <10th percentile.

Statistical methods

Statistical analysis was carried out using Statview or the SAS system 6.12 statistical packages. For continuous variables differences were compared using the student t-test or Mann Whitney U test as appropriate. Chi-square or Fishers exact test (for cell counts <5) were used for comparison between groups. Logistic and multiple regression (as appropriate) were used to determine which variables identified in univariate analysis, had an independent effect on the outcome variables of interest. Relationships between continuous variables were assessed using linear regression or Spearman Rank correlation as appropriate. A p value <0.05 was required for statistical significance.

RESULTS

Antenatal Studies

Study 1: Ninety nine women were recruited to the trial of low dose aspirin versus placebo of whom 65 remained in the study for ≥ 14 days (mean duration of treatment =30 days). Low dose aspirin treatment (n=32) was not associated with an increase in birthweight [1948 (616)g versus 2029 (600)g, p=0.59] when compared with placebo treatment (n=33). There was no difference in the prevalence of SGA babies at delivery, 78% in aspirin treated and 79% in placebo treated. Similarly there was no difference in length [43.1 (4.3) cm versus 43.7 (4.6) cm] or head circumference [31.2 (2.4) cm versus 30.9 (2.7) cm] in aspirin versus placebo treated.

Study 2: Pregnant women with SGA pregnancies and normal umbilical artery Doppler waveforms (n=167) were randomised to twice weekly (n=85) or fortnightly (n=82) tests of fetal surveillance. Women randomised to twice weekly surveillance were delivered four days earlier (264 versus 268 days p=0.04), were more likely to be induced [70 (82%) versus 54 (66%) p=0.01] and less likely to start spontaneous labour [8 (9%) versus 21 (26%) p=0.006] when compared with those randomised to fortnightly surveillance. There was no difference in rates of caesarean section or newborn morbidity (admission to the neonatal unit, hypoglycemia, acidosis at birth) between groups. There was a trend to more SGA babies in the fortnightly [57 (69%) versus 47 (55%) p=0.06] compared with the twice weekly surveillance group.

Study 3: Perinatal outcomes in SGA babies (n=186) were compared between those with normal (n=109) and abnormal (n=77) umbilical artery Doppler studies. The following data are median (10th, 90th percentile) and number (%) as appropriate. SGA babies with abnormal umbilical artery Doppler studies were delivered two weeks earlier [35.8 (29.3, 38.3) versus 38.1 (36.3, 40.1) $p < 0.0001$] were more severely growth restricted at birth [z score birthweight -1.8 (-2.9, -1.3) versus -1.6 (-2.3, -1.2) $p = 0.002$], were more likely to be admitted to the newborn nursery [57 (74%) versus 38 (35%) RR 2.1 (1.6-2.8)] and spent longer in the newborn nursery [15 (0,68) versus 0 (0,11) days $p < 0.0001$] compared with SGA babies with normal umbilical artery Doppler studies. After logistic regression birthweight [OR 7.3 (95% CI 2.2-25) for each standard deviation unit of birthweight below the mean], and gestation at delivery [OR 12.7 (95% CI 5.5-28.6) for babies delivered at < 37 weeks] were independently associated with newborn nursery admission but umbilical artery Doppler status was no longer significant. When compared with mothers of SGA babies with normal umbilical artery Doppler studies, mothers of SGA babies with abnormal umbilical artery Doppler studies were more likely to have preeclampsia [17 (22%) compared with 3 (3%) $p < 0.001$] but there was no difference between groups in maternal size or ethnicity. SGA babies with normal umbilical artery Doppler studies had a trend to more low ponderal indices [53 (49%) versus 27/74 (36%), RR 1.3 (95% CI (1.0-2.0))] compared to those with abnormal Doppler studies. One third of SGA babies with normal umbilical artery Doppler studies were admitted to the newborn nursery and one quarter were hypoglycemic after birth.

Postnatal Studies

Study 4: Two hundred and forty eight babies were recruited to the postnatal studies of whom 203 (82%) had assessments of growth at six months corrected age and 45 (18%) were lost to followup. Forty (20%) were short, 31 (16%) were underweight and 37 (18%) had a low head circumference. Shortness at six months was independently associated with z score birth length [OR 2.6 (95% CI 1.6-4.4) for each standard deviation unit of birth length below the mean], and with male sex [OR 2.8 (95% CI 1.3-6.1) for male infants]. The only variable which was independently associated with low weight at six months was gestation at diagnosis of SGA [OR 8.7 (95% CI 2.6-29.7) for those who were diagnosed SGA at < 34 weeks]. Low head

circumference at six months was independently associated with small head size at birth [OR 4.6 (95% CI 2.6-8.2) for each standard deviation unit of birth head circumference below the mean]. Three quarters of these babies who were short, underweight, or had low head circumferences, also failed to show catchup growth between birth and six months of age, as indicated by a negative Δz score.

Study 5: One hundred and forty eight of the 248 (60%) babies enrolled in the postnatal studies have so far completed neurodevelopmental assessment at 18 months corrected age. SGA babies had lower mean (SD) mental development index scores [95.8 (14.3) versus 100 (15) $p=0.03$] and a higher prevalence of low behavioural rating scores [23 (16%) versus 90/900 (10%) $p=0.04$] when compared with a reference population. An abnormal MDI score was independently associated with not participating in the antenatal SGA studies, [OR 2.7 (95% CI 1.1 – 6.6) for non participants], and with a low birth ponderal index [OR 2.6 (95% CI 1.1-6.4)]. Total PDI score was associated with log newborn nursery stay with a seven unit reduction in PDI for each log unit of nursery stay. A low behavioural rating score was independently associated with low birth head circumference, [OR 2.8 (95% CI 1.5-5.2) for each standard deviation unit of birth head circumference below the mean].

CONCLUSIONS

Antenatal Studies

Study 1: In this study aspirin treatment (100 mg) for a mean of 30 days did not increase birthweight or other parameters of newborn size. These results are consistent with those of two others which have also reported that low dose aspirin did not increase fetal growth in SGA pregnancies. It is now possible to conclude that low dose aspirin is not an effective therapy in SGA pregnancies with abnormal umbilical artery Doppler studies.

Study 2: Planned twice weekly surveillance in SGA pregnancies with normal umbilical artery Doppler studies resulted in earlier delivery and more maternal intervention (induction of labour). Serious maternal and newborn morbidity were uncommon in both arms of this study. A much larger study is necessary to determine whether less frequent surveillance would impact on serious maternal or perinatal morbidity.

Study 3: Abnormal umbilical artery Doppler studies were associated with earlier diagnosis of SGA, more severe growth restriction, earlier gestation at delivery and were not independently associated with newborn nursery admission. Abnormal umbilical artery Doppler studies are therefore markers of a more severe disease process in the SGA baby. SGA babies with normal umbilical artery Doppler studies had a lower rate of newborn morbidity but as 50% were malnourished (low ponderal index), one third were admitted to the nursery and a quarter experienced hypoglycemia, it can be concluded that they are not just normal small babies.

Postnatal Studies

Study 4: A range of perinatal factors were predictive of small size and poor growth at six months of age. Followup of this cohort is ongoing and if the same factors are found to predict continued small size and poor growth at two years of age studies of early intervention aimed at increasing growth in those with perinatal risk factors will be considered.

Study 5: A number of perinatal variables were associated with abnormal test results on the components of the Bayley scales of Infant Development. Further analysis when the whole cohort reaches 18 months of age, will determine whether the same variables are still associated with abnormal neurodevelopmental test results. Followup of the cohort to 36 and 72 months will establish whether Bayley testing at 18 months is predictive of later neurodevelopmental performance. If perinatal factors are still associated with later poor performance, trials of early interventions in those at risk will be justified.

CHAPTER 1

SMALL FOR GESTATIONAL AGE

1.1 TERMINOLOGY

The terminology relating to fetal size and growth is confused. The synonymous phrases 'intrauterine growth retardation' and 'intrauterine growth restriction' (IUGR) refer to the newborn infant that has not achieved its genetic growth potential in utero (Goldenberg & Cliver 1997). The term 'small for gestational age' (SGA) refers to a fetus or a newborn infant that has failed to achieve a specific anthropometric or weight threshold for a specific gestational age (Goldenberg & Cliver 1997). A birthweight <10th percentile is a commonly used classification of SGA (Seeds 1998) and is that recommended by an international working group on definitions of IUGR (Bakketeig et al 1998). There is considerable overlap between IUGR and SGA however they are not synonymous and yet in many publications the terms are used interchangeably.

Surrogate markers of fetal growth and nutrition have been devised, which assess adiposity, but cannot be applied until the time of birth. These include ponderal index [birthweight (g) x 100 / length (cm)³] skin fold thickness, and mid arm circumference, which have been found in a number of studies to be better markers of newborn morbidity than birthweight for gestational age (Walther & Ramaekers 1982, Sasanow et al 1986, Patterson & Pouliot 1987). A recent study in an English population (Sanderson et al 1994) found that 37% of SGA babies (birthweight <10th percentile) had evidence of malnutrition (ponderal index <10th percentile). Seven percent of appropriate for gestational age (AGA) babies (birthweight >10th percentile) had a

low ponderal index. The results are almost identical to those found in an older study (Walther & Ramaekers 1982) where 38% of SGA babies had a ponderal index <10th percentile and 8% of appropriate weight for gestational age babies had a low ponderal index. The results of these studies support the commonly held belief that a number of SGA babies are not malnourished but are constitutionally small, representing the tail end of a normal distribution.

Clinicians would prefer to use classifications of size at birth which predict the small babies which are undernourished and more likely to experience morbidity. Wilcox et al (1993) have tried to do this by developing the individualised birthweight ratio which is a ratio of actual birthweight to predicted birthweight. Predicted birthweight is computer generated using a mathematical formula which incorporates factors known to affect birthweight (gestation, maternal height, weight, ethnic group and parity). The individualised birthweight ratio has been reported to be a better predictor of the undernourished fetus (as measured by a low skin fold thickness or low ponderal index) than uncorrected weight for gestational age and may therefore be a better predictor of IUGR (Sanderson et al 1994). Using the individualised birthweight ratio, 63 of 306 (21%) SGA infants (birthweight <10th percentile) were reclassified as having normal birthweight and 3% (78/2440) of babies with birthweight >10th percentile were reclassified as SGA (Sanderson et al 1994). Those babies reclassified as normal had a similar rate of perinatal complications (abnormal fetal heart patterns, operative delivery for fetal distress, neonatal resuscitation) as those originally classified as normal. Babies reclassified as small had a significantly higher rate of the above complications compared to those reclassified as normal.

Customised fetal growth and birthweight standards have been generated by Gardosi et al (1995). By using variables known to affect fetal weight (maternal height, weight, ethnicity, parity, and smoking status) and incorporating them into a computer programme in the second trimester of pregnancy (after a dating scan), a customised fetal growth curve, which displays weights for gestation and projected birth weight, can be calculated for each woman. Customised birthweight less than the tenth percentile was a better predictor of caesarean section for fetal distress and newborn morbidity than weight for gestational age <10th percentile (de Jong et al 1998).

Customised or individualised birthweight standards may be better predictors of newborn morbidity and growth restriction than unadjusted weight for gestational age. However these methods are more complicated and require sophisticated technology. Applications of these methodologies to different populations have not yet been reported. It is likely that the mathematical formulae to adjust birthweight will need to vary in different settings. For these reasons customised birthweight standards have not been incorporated into general obstetric practice but they may have a role in the future.

As outlined above, in the absence of a simple and reliable technique for identifying the fetus or newborn which has failed to reach its growth potential, many studies of fetal growth still use birth weight for gestational age <10th percentile as the main outcome measure. This is the definition of SGA used in this thesis.

1.2 PHYSIOLOGY OF THE REGULATION OF FETAL GROWTH IN NORMAL PREGNANCY

The primary determinant of fetal growth in late gestation is the ability of the uteroplacental unit to deliver oxygen and nutrients to the fetus (Gluckman 1997).

The major factors which influence fetal tissue uptake of nutrients are listed below:

- maternal nutrition
- uterine blood flow
- placental transfer
- umbilical-placental blood flow
- fetal endocrine status

1.2.1 Maternal Nutrition

Healthy women, eating an unrestricted diet, are able to meet the needs for fetal growth and development by at most a six to nine percent increase in their pre-pregnancy caloric intake (Viteri et al 1989). The requirements for extra calories are low in the first trimester (estimated 15 kcal/day) increase in the second trimester (estimated 120 kcal/day) and are greatest in the third trimester (estimated 310 kcal/day) corresponding to the period of maximum fetal weight gain (Roberts and Young 1988).

1.2.2 Uterine Blood Flow

Early in the first trimester of pregnancy systemic vasodilatation occurs which is associated with a fall in afterload and vascular filling pressure leading to an increase in cardiac output and increase in blood volume (Duvekot et al 1993). This high flow,

low resistance circulation persists throughout normal pregnancy and is one of the factors which contributes to the increased uterine blood flow during pregnancy.

The human placenta receives its blood supply from more than 100 uteroplacental or spiral arteries (Brosens & Dixon 1966). These vessels are converted from small muscular arteries to large dilated vascular channels by a process of trophoblast migration and replacement of the endothelium and muscular media (Brosens et al 1967). In normal pregnancy these changes occur throughout the spiral arteries, from the point where they open into the intervillous space to where they originate from their parent radial arteries, in the inner third of myometrium (Brosens et al 1967). It is now thought that this vascular replacement occurs in two phases. Firstly the conversion of the decidual segments of the spiral arteries which occurs by a wave of endovascular trophoblast migration occurring late in the first trimester. The process is completed by further trophoblast migration into the myometrial segments of the spiral arteries. The latter phase of trophoblast migration predominantly occurs in the second trimester (Robertson et al 1975) but may continue into the third trimester (Pijnenborg et al 1991). In normal pregnancies this physiological conversion has occurred in over 90% of spiral arteries by the end of pregnancy (Ghidini et al 1998).

Recently the microscopic anatomy of endovascular invasion has been reviewed in detail (Damsky & Fisher 1999). Early in pregnancy the conceptus is surrounded by a cytotrophoblastic shell and does not have contact with the maternal circulation. Before contact with the uterine circulation can occur the embryo needs to anchor itself to the uterine wall and release maternal blood into the intervillous space. The development of this haemochorial placenta depends on the differentiation of the

cytotrophoblast cells contained in the two types of chorionic villi (floating and anchoring). The cytotrophoblast cells in the floating chorionic villi differentiate into syncytiotrophoblasts whose primary function is transport and exchange between the maternal and fetal compartments. Other cytotrophoblasts differentiate and aggregate into columns to form anchoring chorionic villi which firstly become attached to the uterine wall (Zhou et al 1997¹). These cytotrophoblast cells then proceed to invade the uterine stroma and the spiral arteries (fig 1.1).

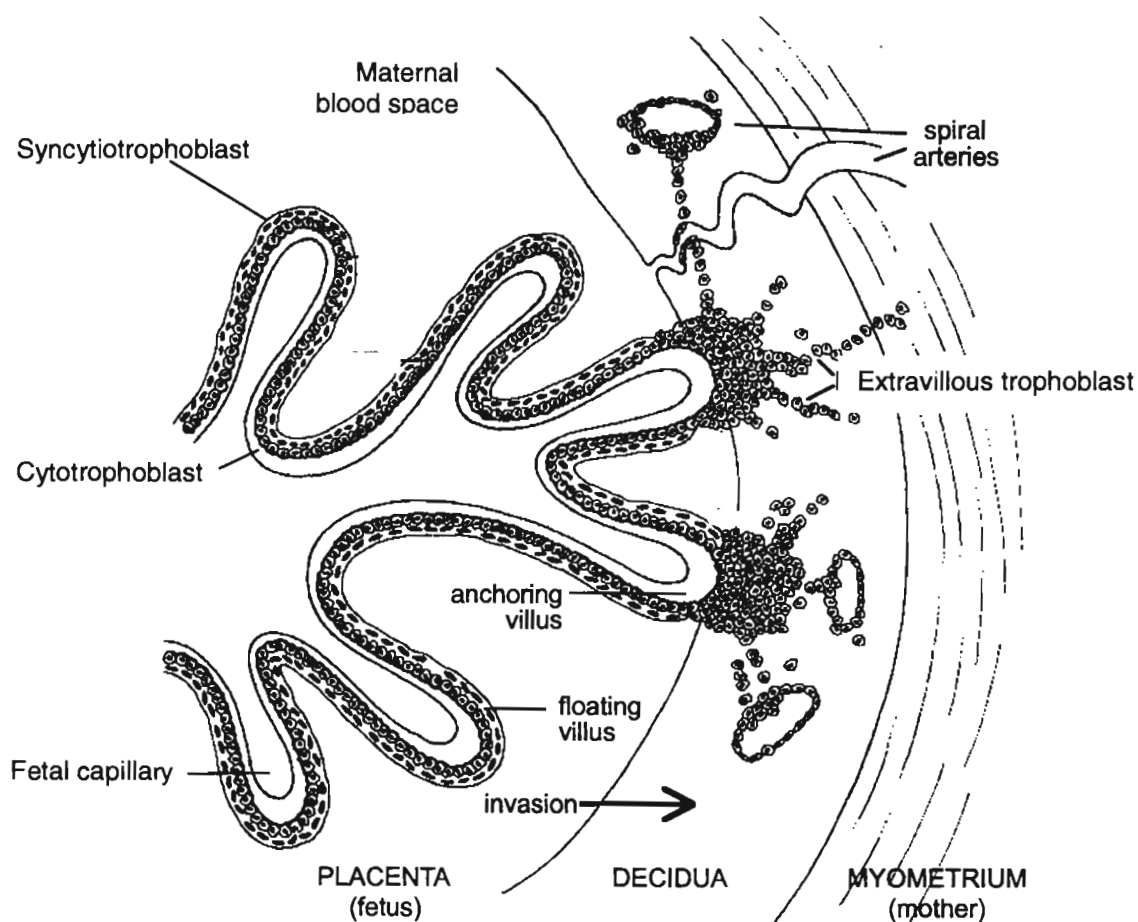


Fig 1.1: Diagrammatic representation of cytotrophoblast invasion of uterine stroma and spiral arteries (modified from Jaffe et al 1998)

During this process masses of invasive cytotrophoblasts breach the spiral arteries and as they move in a retrograde fashion replace the maternal endothelium and the muscular media. This endovascular invasion converts the previously small bore, high resistance arteries into hugely dilated uteroplacental vessels which are able to accommodate the massive increase in uterine blood flow (600 mls/min at term). The endovascular invasion stops at the junction between the inner third and outer two thirds of the myometrium and does not occur in the veins.

The exact mechanisms which stimulate subpopulations of cytotrophoblasts to leave the placenta and take over maternal blood vessels are still not fully understood.

Evidence is increasing which suggests that as invasive cytotrophoblasts differentiate from cytotrophoblast stem cells they transform their adhesion receptor phenotype so as to resemble the endothelial cells they replace (Zhou et al 1997¹). It is hypothesised that this switch in adhesion receptors allows maternal and fetal cells to cohabit in the hybrid uteroplacental vessels in normal pregnancy (Damsky et al 1998). Important changes also occur in the expression of extracellular matrix degrading proteinases (Fisher et al 1989) which enhance invasiveness in vitro (Librach et al 1991). Up-regulation of tissue inhibitors of these proteinases has been demonstrated in an in vitro study (Bass et al 1997) and is likely to be a balancing mechanism which limits cytotrophoblast invasion. Studies in mice have indicated a maternal decidual component in the production of proteinase inhibitors (Alexander et al 1996) but there is currently no human data to determine the extent of maternal involvement in this process.

Recent experiments have shown that oxygen tension is important in determining whether cytotrophoblasts differentiate to proliferate or invade (Genbacev et al 1997). Prior to the establishment of the uteroplacental circulation (<10 weeks) the conceptus is relatively hypoxic with low mean oxygen pressure in the intervillous space (Rodesch et al 1992). In recent experiments, using human anchoring villus explants at six to eight weeks of gestation, control explants were maintained in 20% or 8% oxygen culture conditions (Genbacev et al 1997), mimicking the environment near the uterine arterioles (fig 1.2 Zone V).

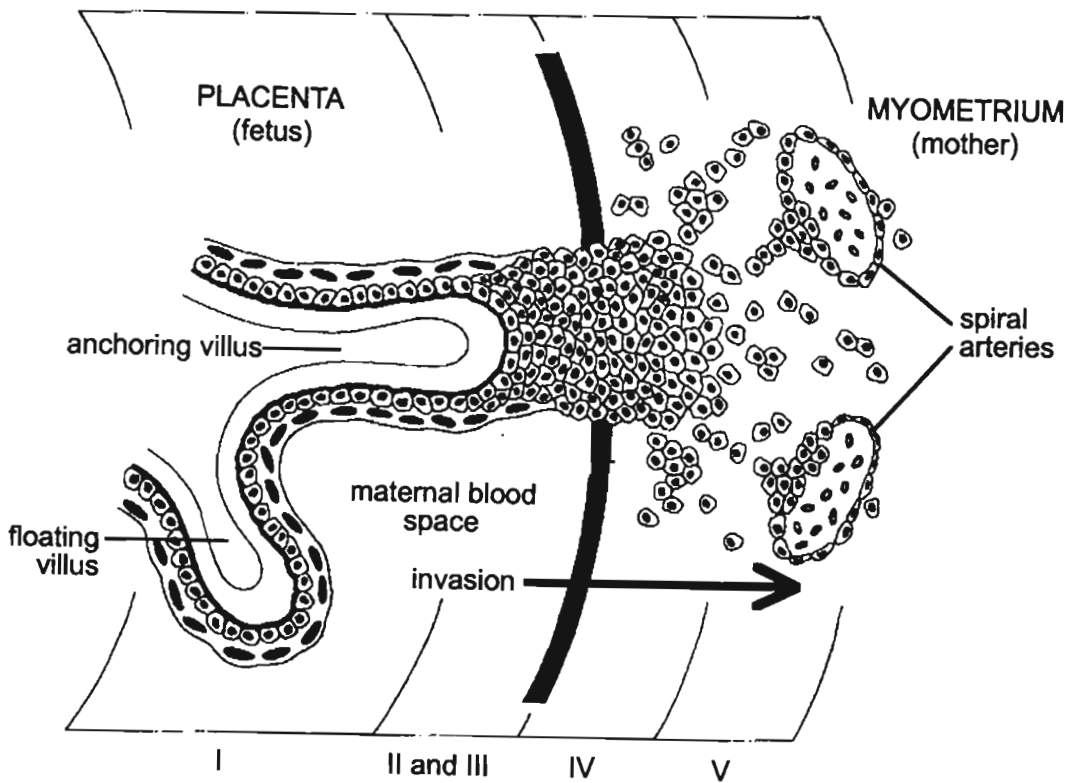


Fig 1.2 Section through a chorionic villus at the fetal-maternal interface at 10 weeks gestation. I, II, III, IV and V refer to zones. Floating chorionic villi suspended in the intervillous space (zone 1), anchoring chorionic villi form cell columns of cytotrophoblasts (zone II and III) which invade the decidua (zone IV) and spiral arteries (zone V). Modified from Redman 1997

Other villi were cultured in 2% oxygen mimicking the hypoxic conditions in the fetal compartment near the uterine lumen in the intervillous space (fig 1.2 Zone I). Cytotrophoblasts cultured in 20% and 8% oxygen altered their expression of adhesion receptors and became highly invasive. Those cultured in hypoxic conditions (2% oxygen) continued to proliferate, did not alter their expression of adhesion receptors and did not invade. This hypoxic environment likely promotes the early growth of the placenta whereas once interstitial invasion begins the invasive cytotrophoblast meets a positive oxygen gradient which favours further differentiation and invasion (Damsky & Fisher 1998).

1.2.3 Placental Transfer

Having established a haemochorial placenta, the maternal and fetal circulations are separated only by the endothelium and lamina basalis of the fetal capillaries as well as fetal villous tissue (lamina basalis, cytotrophoblast and syncytiotrophoblast cells).

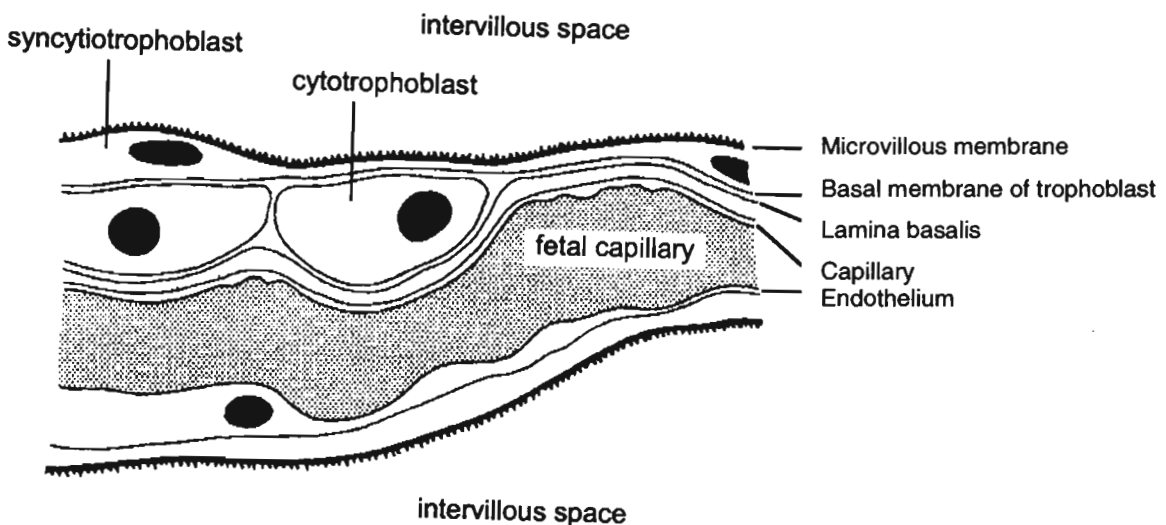


Fig 1.3 Diagrammatic representation of the placental barrier between the maternal and fetal circulations

The syncytiotrophoblast is the cell primarily responsible for the transfer of respiratory gases and nutrients. The maternal surface of the syncytiotrophoblast is covered by a microvillous membrane which contains the main receptors and transporters as well as ion channels (Boyd et al 1994). The mechanisms involved in the transfer of various substances across the placenta are summarised in fig 1.4.

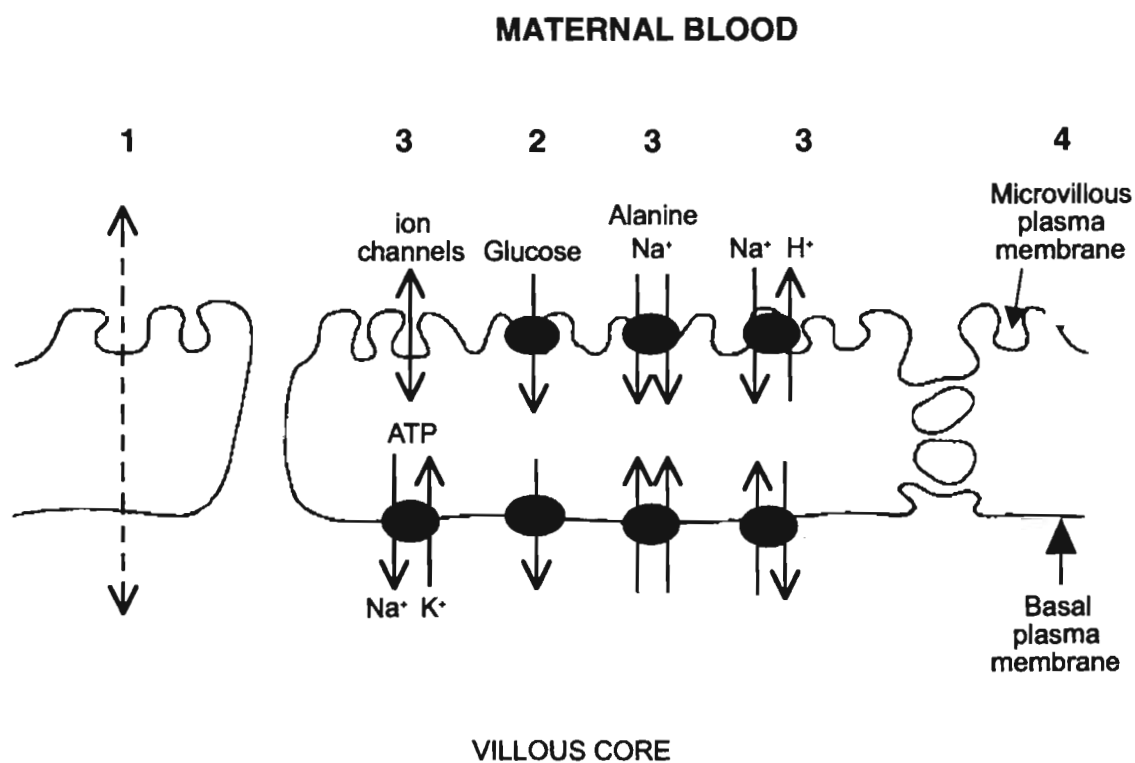


Fig 1.4 Diagram of the four major mechanisms of transfer of solute across the placenta. 1=simple diffusion, 2=facilitated diffusion, 3=active transport, 4=endocytosis. *Modified from Sibley et al 1997.*

Simple diffusion is limited by placental blood flow and exchange area. Oxygen, carbon dioxide and urea are transferred in this way. Facilitated diffusion is carrier mediated (e.g glucose, lactate) but as the transfer occurs down an existing concentration gradient additional energy is not required. Active transport involves carrier proteins on the cell surface and extra energy (e.g amino acid transfer).

Receptor mediated endocytosis is utilised to transfer large molecules e.g. IgG. The factors which control the regulation of placental transport of various nutrients are currently not well understood in the human (Boyd et al 1994, Sibley et al 1997). Glucose transporter I (GLUT1) is thought to be responsible for glucose transport between mother and placenta and GLUT3 is thought to be important for glucose transport from placenta to fetus (Zhou and Bondy 1993). IGF-I may have a role in the regulation of GLUT-1 and 3 as maternal treatment with IGF-I (in the sheep) increases messenger RNA for both glucose transporters (Bauer et al 1998). The placenta is a metabolically active organ and in a study of perfused human placentae utilisation of glucose by the placenta was found to be 50-60% which results in approximately 50% remaining available for fetal use (Hauguel et al 1986).

1.2.4 Umbilical-Placental Blood Flow

In normal pregnancy there is progressive growth of the placental villous tree, accompanied by corresponding growth and increase in cross sectional area of the placental arterial and capillary circulations resulting in a vasculature with low impedance (Kaufmann 1982). The failure of an isolated placental cotyledon to dilate in response to vasodilator prostaglandins suggests that under normal circumstances the placental circulation is maximally dilated (Glance et al 1986). Placental blood flow is influenced by a number of factors including fetal cardiac output, humoral factors (which could alter placental impedance), and the structural organisation of the placental arterial circulation (Poston 1997). The placenta normally receives about 50% of the fetal cardiac output and this proportion is dependent on fetal blood pressure and systemic vascular resistance (Dawes 1971).

The sheep fetus is well adapted to preserve the blood supply to the placenta. Under hypoxic situations peripheral vascular beds vasoconstrict and blood supply to the brain, adrenals, heart and placenta are increased (Cohn et al 1974). Doppler studies in hypoxic human fetuses also confirm evidence of peripheral vasoconstriction and centralisation of flow (Bilardo et al 1990).

The fetoplacental circulation lacks autonomic innervation and vascular tone is therefore dependent on autocrine and circulating vasoactive factors (Poston 1997). There are several vasoactive compounds produced by the umbilical vessels and/or placental tissues. In vitro studies, using a variety of perfused placental models or strips or rings of isolated umbilical vessels, have identified that a number of these agents vasoconstrict or dilate the fetoplacental vessels. Various autoids can also interact and stimulate the synthesis of each other to influence overall impedance.

Thromboxane and endothelin induce a powerful vasoconstricting response in the placental vasculature. Thromboxane is produced by the umbilical arteries and likely has a role in the constriction of these vessels after birth (Templeton et al 1991). The main source of thromboxane production within the placenta is thought to be from aggregating platelets (Poston 1997).

Three endothelin peptides have been described (ET-1, ET-2, ET-3) which are produced from endothelial cells. Endothelin receptors are found throughout the placental vascular tree (Kohnen et al 1997). ET-1 and ET-2 produce potent and long lasting vasoconstriction of the fetoplacental resistance vasculature (MacLean et al 1992) and ET has been shown to constrict placental veins. The endothelins may

have a physiologic role in the control of the fetoplacental circulation (MacLean et al 1992). The high concentrations in fetal blood could also indicate a role in fetal development as the endothelins are also growth factors (Poston 1997).

Prostaglandin $F^2\alpha$ is a less potent vasoconstrictor in the placental circulation (McCarthy et al 1994). Systemic vasoconstrictors (e.g catecholamines, angiotensin II, oxytocin and vasopressin) in general have minimal or weak effects on the fetoplacental arteries (Poston 1997) and will not be considered in further detail.

Prostacyclin induces fetoplacental relaxation (Maigaard et al 1986) and is synthesised by the umbilical vessels. Infusion of indomethacin did not alter resting pressure in the perfused cotyledon suggesting that eicosanoid synthesis is not the major determinant of resting placental tone (Glance et al 1985).

Atrial natriuretic peptide (ANP) is produced by the fetal heart and may also have a role in the regulation of fetal placental blood flow. It is found in cord blood, receptors are present in the placenta (McQueen et al 1990¹) and in vitro it dilates the placental cotyledon precontracted with angiotensin II (McQueen et al 1990²).

Recent studies suggest that the potent vasodilator nitric oxide (NO) may have the most important role in the maintenance of low placental vascular impedance in normal pregnancy (Myatt et al 1991, Myatt 1992). NO is generated from the metabolism of L-arginine by the enzyme nitric oxide synthase (NOS). In endothelial cells NO diffuses to underlying smooth muscle cells where it activates guanylate cyclase and increases production of cyclic guanosine monophosphate which causes smooth muscle relaxation (Myatt et al 1991).

The endothelial form of nitric oxide synthase (eNOS) is found in the endothelium of the umbilical chorionic plate and stem villous vessels but not in the terminal villous capillary endothelium of normal placentae (Myatt et al 1993). It is also found in the syncytiotrophoblast (Buttery et al 1994).

Blood flow (shear stress) is a powerful stimulus for NO release in the placental vascular bed. In a perfusion arteriograph model, incremental increases in intraluminal flow resulted in dilatation of stem villous arteries. Inhibition of NOS prevented the flow induced dilatation (Learmont & Poston 1996).

Inhibition of NO by methylene blue increases perfusion pressure in the isolated cotyledon (Myatt et al 1991). Glyceryl trinitrate stimulates NO production and vasodilates the placental circulation which has been precontracted with the thromboxane analogue U46619 (Myatt et al 1991). NO generated by the addition of glyceryl trinitrate also attenuates the vasoconstrictor effects of endothelin-1 in the placental circulation (Myatt et al 1992). NO may therefore also have an important role in modulating the effects of vasoconstrictors. The fact that inhibition of NO synthesis or action increases perfusion pressure whereas inhibition of prostaglandin synthesis does not suggests that NO has a more important role in the regulation of human fetal placental vascular impedance than the eicosanoids (Myatt 1992).

1.2.5 Endocrine Regulation Of Fetal Growth In Normal Pregnancy

a) *Insulin like growth factors*

There is increasing evidence that the insulin like growth factors (IGFs) are important regulators of fetal growth. The two main IGFs (IGF-I and II) are single chain polypeptides, similar in structure to proinsulin and relaxin. These growth factors and the genes encoding them are found in many tissues, hence confirming their role as paracrine or autocrine factors. They stimulate insulin-like metabolic effects, e.g glucose uptake by cells and they also stimulate cell replication and differentiation (Hills & Chard 1995). Their actions are mediated through two types of receptors: type I IGF receptor which preferentially binds IGF, and the type II receptor which preferentially binds IGF-II. These receptors are widely distributed throughout the body and are present from very early in pregnancy. The human placenta contains a high density of IGF-I receptors. IGF-I and II have been shown to stimulate 3β hydroxy steroid synthesis in cytotrophoblasts in vitro and may have a role in the maintenance of placental progesterone production (Nestler 1989).

IGF-I messenger RNA can be identified from preimplantation human embryos five to eight days after conception (Hemmings et al 1992). IGF-II is detectable in amniotic fluid from 10-12 weeks gestation indicating local production by fetal membranes and also a possible role in early fetal growth (Nonoshita et al 1994). Expression of IGF-II is less later in gestation and it is thought it may have an important role early in pregnancy when it stimulates protein synthesis and mitogenesis (Guevara-Aguirre 1996). IGF-I has the predominant influence in the fetal phase of growth and in the perinatal period (Gluckman 1997). There is a strong correlation between IGF-I levels

in venous cord blood and birthweight which suggests a direct relationship between IGF-I and the control of fetal growth (Verhaeghe et al 1993).

In fetal sheep IGF-I is acutely regulated by glucose but not amino acids (Oliver et al 1993). Insulin elevates and pancreatectomy reduces IGF-I levels (Gluckman et al 1987). It is therefore proposed that the primary regulation of IGF-I in the fetus is via glucose and insulin (Gluckman 1997) (fig 1.5). Placental transfer of glucose determines fetal insulin secretion which in turn determines fetal IGF-I secretion.

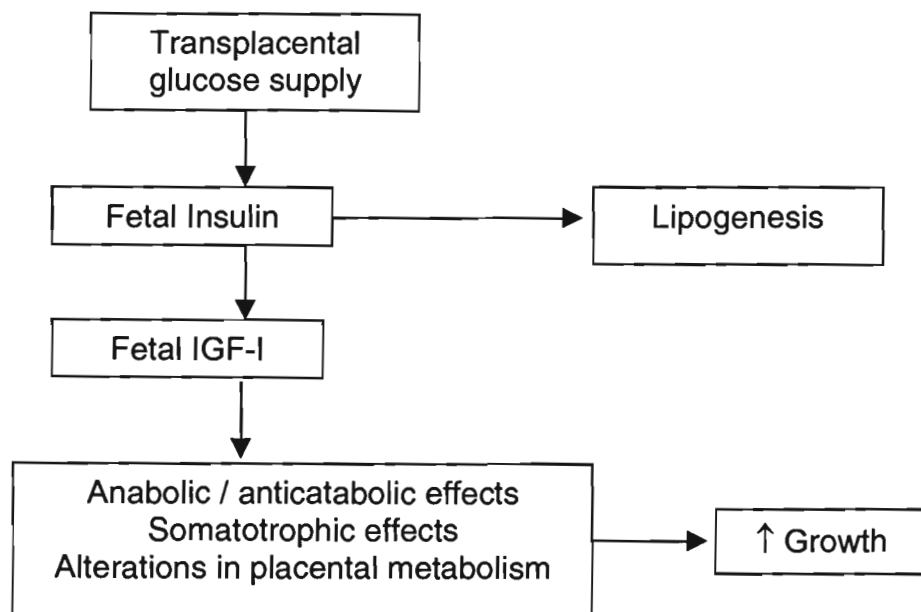


Figure 1.5: Major fetal endocrine factors influencing fetal growth and anabolism in late pregnancy

In the circulation most IGF is bound to IGF binding proteins, predominantly to the growth hormone dependent IGF binding protein 3 (IGFBP-3). This complex, which is produced in the liver, is thought to act as a reservoir for, and to extend the half life of,

circulating IGFs (Hills and Chard 1995). Serum IGFBP-3 levels are low at birth and rise postnatally. In tissues IGFs are bound to lower molecular weight IGFBPs (mainly IGFBP-1 and IGFBP-2) which modulate the action of IGFs and transport them into their target cells. IGFBPs are expressed in most fetal tissues from 14 weeks gestation. IGFBP-1 in adults is regulated by insulin and dietary factors (Hills & Chard 1995) whereas IGFBP3 is regulated by growth hormone (Giudice et al 1995). There is an inverse correlation between IGFBP-1 level in cord blood and birthweight (Wang et al 1991, Verhaeghe et al 1993).

Maternal studies

Maternal and fetal IGF-I are independent of each other. There is no correlation between maternal and umbilical cord serum IGF-I levels (Wang et al 1991, Hills et al 1996) and in rat studies radiolabelled IGF did not cross from mother to fetus (Davenport et al 1990). Maternal IGF-I has been shown in a number of human studies to increase with advancing gestation (Wilson et al 1982, Holmes et al 1997, Holmes et al 1998). Some studies have reported a correlation between maternal IGF-I and birthweight (Hall et al 1984, Caufriez et al 1993) but most have not (Wang et al 1991, Hills et al 1996, Holmes et al 1997, Holmes et al 1998)

Maternal circulating levels of IGFBP-1 increase in early pregnancy, peak at 12 to 13 weeks and high concentrations persist until term (Wang et al 1991). Levels of IGFBP-1 are inversely correlated with maternal weight (Baldwin et al 1993). Much of the maternal IGFBP-1 is thought to be secreted by the decidua and maternal IGFBP-1 may be an important maternal regulator of fetal growth (Chard et al 1994).

Maternal IGFBP-3 has been reported to increase with gestational age but its role in human pregnancy is still unclear (Holmes et al 1997).

Placenta

Placental transfer of glucose and amino acids are carrier mediated but the factors important in the regulation of these carriers are not well understood. In sheep, infusion of IGF-I levels to the mother resulted in an increase in fetal glucose levels, increased placental amino acid uptake and increased placental lactate production (Liu et al 1994). IGF-I infusion in the fetal sheep reduced amino acid uptake by the placenta resulting in increased availability to the fetus (Harding et al 1994). The results of these two studies suggest that in the sheep both maternal and fetal IGFs are important in the regulation of placental uptake of nutrients and in the partitioning of nutrients between mother, placenta and fetus.

The variability in IGF levels reported by different investigators is likely due to methodological problems, as a number of publications have been based on inadequately validated IGF measurements (Bang et al 1994, Consensus statement). IGFBPs interfere with measurement of IGF in plasma samples. IGFBPs therefore need to be efficiently extracted from samples prior to performing assays for IGFs (Breier et al 1990).

b) Other hormones and growth factors

Although IGF-I has a very important role in fetal growth in late pregnancy, additional hormones and/or nutrients are also important (Bauer et al 1998). Insulin was originally thought to be the most important fetal growth hormone in late pregnancy.

Fetal hyperinsulinemia, secondary to fetal hyperglycemia in maternal diabetes, is associated with macrosomia, which is largely due to fat deposition (Fowden 1995). Even though insulin can directly stimulate cell division in early pregnancy (Hill 1989) it is now thought that the main action of insulin is to promote fetal growth via alteration in cellular uptake of glucose and increased IGF-I production (Gluckman 1986).

Growth hormone appears to have a small effect on fetal size, as growth hormone deficiency at birth is associated with only a small reduction in length (Gluckman et al 1992). After birth growth hormone is an important regulator of IGF-I and II (Hills and Chard 1995) and mutations in the growth hormone receptor gene result in profound postnatal growth restriction (Rosenfeld et al 1994). The placental syncytiotrophoblast cells secrete a variant of growth hormone (hGH-v) into the maternal circulation which suppresses maternal pituitary growth hormone release. hGH-v is the dominant form of circulating growth hormone in the second half of pregnancy (Bauer et al 1998). Levels of hGH-v and maternal IGF-I concentrations correlate suggesting that hGH-v may regulate maternal IGF-I (Mirlesse et al 1993). hGH-v may enhance placental diffusion capacity (Harding et al 1996) but as it does not cross the placenta its actions are restricted to the maternal and placental compartments (Bauer et al 1998). It has also been reported to induce maternal insulin resistance which may encourage glucose transfer to the fetus (Gluckman 1997).

Human placental lactogen is secreted into both maternal and fetal circulations, however whether it has an important role in the regulation of human fetal growth is still unknown (Gluckman 1995). The thyroid hormones also contribute to fetal growth (Fowden et al 1995) and congenital hypothyroidism can be associated with small size

at birth. Thyroid hormones may have a direct effect on fetal growth as well as an effect mediated by IGF (Fowden et al 1995).

Epidermal growth factors (EGF) and transforming growth factor α (TGF α) have different genes and amino acid sequences but share the same receptors and have the same biological actions (Styne 1998). TGF α is produced by maternal decidua early in pregnancy and is transported to the fetus. It may have an important role in placental implantation and growth (Styne 1998). EGF receptors are located on the outer membrane of syncytiotrophoblast cells at the fetomaternal interface (Duello et al 1994). EGF and TGF α are necessary for cytotrophoblast cell division. TGF α and EGF are also important for growth and differentiation of a number of fetal organs including gut, brain and skin (Styne 1998).

1.3 PATHOPHYSIOLOGY OF SGA

SGA babies are a heterogeneous group. A simple classification system has been proposed by Gluckman & Harding (1997) and endorsed by others (Lapillone et al 1997). Gluckman and Harding (1997) divided SGA babies into four main categories. Babies in the first category have no demonstrable maternal or fetal pathology, but fall at the lower end of the normal distribution of weight for gestational age. They are described as being constitutionally small. Maternal characteristics of these children include an over representation of first pregnancies, smaller mothers and if birthweight charts are not sex specific, female infants. In the second category, genetic, chromosomal or congenital abnormalities retard fetal growth, often from early in pregnancy, resulting in the birth of a SGA baby. Common examples include the trisomies, abnormalities like Potters Syndrome, and severe congenital heart disease.

Prenatal genetic diagnosis using insitu hybridisation with DNA probes has enabled the detection of previously unrecognised chromosomal abnormalities. Mosaicism confined just to the placenta has been identified in 7/108 (7%) of cases of early onset fetal growth restriction referred for prenatal diagnosis (Wolstenholme et al 1994). In a recent series of 35 pregnancies with severe IUGR that underwent prenatal diagnosis two cases of uniparental disomy of chromosome 16 were identified (Moore et al 1997). Severe IUGR has also been reported in association with a mutation of the gene encoding IGF-I (Woods 1997).

In the third category of SGA toxic agents are responsible for the growth restriction. Examples here include infectious or teratogenic agents like rubella and cytomegalovirus, as well as drugs (e.g tobacco, alcohol, cocaine). In the fourth and largest category substrate limitation (from a range of causes) reduces fetal growth (table 1.1).

Table 1.1: Possible mechanisms interfering with transfer of nutrients to the fetus

Mechanism	Pathological Process	Underlying condition or pregnancy complication
Under nutrition	Reduced availability of nutrients to fetus	Famine Anorexia nervosa Malabsorption
	Defective trophoblast replacement of spiral arteries	Preeclampsia Idiopathic IUGR
Reduced uteroplacental perfusion	± secondary occlusion of lumen (acute atherosclerosis)	Abruption Placental infarction
	Smooth muscle hyperplasia	Chronic hypertension
	Fibrin deposition, vasculitis	antiphospholipid syndrome
Abnormal placenta	Placental vascular or villous pathology	IUGR
	Developmental abnormality	Placental haemoangioma Velamentous insertion of cord

1.3.1 Maternal Under-nutrition

Maternal weight gain during pregnancy is a surrogate marker of maternal nutrition. In a meta-analysis of 61 papers which have studied the effect of gestational weight gain on birthweight, a weight increase of <7 kg in a well nourished woman was associated with a relative risk of IUGR of 2 (Kramer 1987). The magnitude of effect of low gestational weight gain on birth weight was more pronounced where women were also undernourished accounting for up to one third of cases of IUGR (Kramer 1987).

Epidemiologic studies of women delivering babies during the Dutch famine in the second world war has revealed the extent to which fetal size is affected by severe maternal under-nutrition (Smith 1947). From January to April 1945 food was rationed. Caloric intake was restricted to about 1100 calories per day for women living in the main Dutch cities. Up until this time the population had been well fed. A ten percent reduction in birthweight (240 gm median) was found but only in women exposed to famine in the third trimester of pregnancy when fetal weight increase is most pronounced. A recent English prospective observational study has also shown that reduced protein intake in late pregnancy was independently associated with reduced birthweight (Godfrey et al 1996)

1.3.2 Uteroplacental Perfusion In SGA Pregnancies

A reduced supply of nutrients secondary to reduced uteroplacental perfusion is the commonest underlying mechanism of poor fetal growth. This is seen when growth restriction occurs in association with preeclampsia, other vascular disorders and in many cases of so called idiopathic fetal growth restriction. Evidence for reduced uteroplacental perfusion comes from older studies which used radioisotopes (Karr et

al 1980, Nylund et al 1983). In the first study the mean intervillous blood flow in 11 women with SGA babies was significantly less [109 (34) versus 140 (53) ml/min/100ml of intervillous space] than in those with AGA babies. In the later report, the median blood flow index in 19 patients with IUGR (without preeclampsia) was less than half that in the control group with normal fetal growth. Modern imaging technology using magnetic resonance imaging has also demonstrated evidence of reduced placental perfusion in pregnancies with IUGR (Francis et al 1998).

The findings of reduced uteroplacental perfusion in the radioisotope and magnetic resonance imaging studies are confirmed by the results of several histologic studies which have demonstrated pathologic changes in the uteroplacental vessels in pregnancies with IUGR. Histologic specimens have been obtained from placental bed specimens taken at hysterectomy, by placental bed biopsy at caesarean section, and also from histological examination of the basal plate of the placenta after delivery (Sheppard & Bonnar 1981, Pijnenborg et al 1986, Khong et al 1986). In 24 IUGR pregnancies without hypertension reviewed by Khong et al (1986), 19 (80%) had no physiologic changes present in myometrial segments of spiral arteries (evidence of superficial physiologic change only). In ten cases (42%) no physiological changes were identified in the decidual or myometrial segments (complete absence of physiologic changes). In another series of 11 cases of IUGR (Sheppard & Bonnar 1981) only three (27%) showed physiological changes in both the myometrium and decidua. Similar findings were reported by Olofsson et al (1993) who found that nine of 12 SGA pregnancies had absent physiologic changes in spiral arteries from placental bed biopsies. These pathological features are identical to those seen in pregnancies with preeclampsia (Khong et al 1986) (fig 1.6). In addition Khong et al

identified intraluminal trophoblast in the uteroplacental arteries of some (number not specified) third trimester IUGR and preeclamptic pregnancies. Intraluminal trophoblast might further impair uteroplacental perfusion and is not encountered in normal pregnancy. The IUGR pregnancies reported in these histological studies are likely to have been at the severe end of the disease spectrum (Khong et al 1986). However there are no placental bed biopsy data available from less severely growth restricted pregnancies.

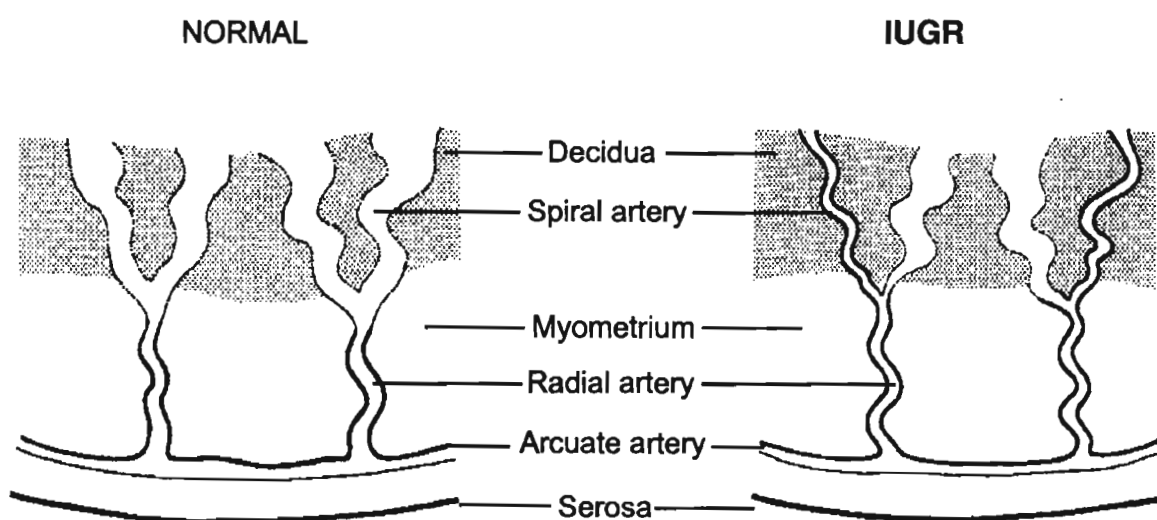


Fig 1.6 Diagrammatic representation of the physiologic changes in the spiral arteries in normal pregnancy compared with pathological changes commonly found with IUGR pregnancy

Recent microscopic studies of cytotrophoblast invasion in pregnancies with preeclampsia have shown that floating chorionic villi appear normal, but differentiation of invasive cytotrophoblast is abnormal (Zhou et al 1997²). Invasive cytotrophoblasts obtained from placental bed biopsies from women with preeclampsia retain expression of adhesion receptors characteristic of the stem cells from which they originated (Zhou et al 1997²). Unlike cytotrophoblasts from normal

pregnancy (Zhou et al 1997¹) they do not turn on the receptors which promote invasion and/or an endothelial phenotype. It is thought that this failure to express a normal vascular adhesion phenotype may be responsible for the superficial invasion and sometimes complete lack of invasion which is seen in the spiral arteries of women with preeclampsia. This failure of differentiation may be induced by hypoxia (Damsky & Fisher 1998). As the same pathological features are found in placental bed biopsies from pregnancies with idiopathic IUGR it is conceivable that the same lack of differentiation to a vascular adhesion phenotype may also occur in IUGR pregnancies. Currently there are no similar studies in IUGR pregnancies without preeclampsia.

1.3.3 Placental Transfer In SGA Pregnancies

The placenta plays a pivotal role in fetal growth. It must integrate signals from the fetus and the mother in an attempt to match fetal demand with maternal substrate supply. At the same time it must meet its own high metabolic demands as well as transfer fetal waste products back to the mother. In pregnancies with small for gestational age babies, placental weight is reduced (Fox 1994). In a report of placental pathology in term SGA pregnancies compared to term appropriate for gestation age controls, placental weight in SGA was found to be over 100 gm less (428 ± 86 versus 563 ± 106 $p < 0.001$, Salafia et al 1992). It is not established whether the baby is small because the placenta is small, or whether the placenta is small for the same reason which resulted in a small baby. It is known that a normal placenta has considerable reserve as pathological processes which reduce functional placental mass by 30 to 40% may not affect fetal growth (Fox 1995).

There is limited information available about placental transport of specific nutrients in pregnancies with fetal growth restriction (Sibley et al 1997). Glucose transporter activity has been studied in placentae from human pregnancies with IUGR (Jansson et al 1993). No difference was found in glucose uptake or glucose transporter expression between normal pregnancy and those with IUGR but further studies are required. There is evidence to suggest that placental amino acid transport is reduced in human pregnancies with IUGR (Dicke & Henderson 1988). This reduced transport may be due to reduced numbers of amino acid transporters in SGA placentae (Grey et al 1995). Whether alterations in amino acid transport is a cause or effect of poor growth is not understood and further research is necessary.

Placental transfer is also potentially reduced by any pathological process which interferes with transfer across the villous membrane (fig 1.3). Cytotrophoblastic hyperplasia and thickening of the basement membrane has been reported in pregnancies with IUGR and is thought to be a response to ischaemia secondary to reduced uteroplacental perfusion (Salafia et al 1992).

Chronic villitis has been associated with IUGR (Labarrere et al 1985, Salafia et al 1992) and has been found more commonly in SGA (38/128, 30%) than AGA (34/179, 19%) placentae ($p < 0.05$) (Salafia et al 1992). The pathological lesions in this condition include an inflammatory cell infiltrate of the villous stroma by lymphocytes (30 to 50% of maternal origin), fibrinoid necrosis, villous oedema, avascular villi, endovasculitis and thrombosis of fetal capillaries. Lesions can be focal or diffuse and usually involve the terminal or tertiary stem villi (Knox & Fox 1984). It was originally thought that chronic villitis was due to a viral infection, however cultures failed to

show an aetiological agent (Altshuler et al 1975). More recently it has been proposed that chronic villitis may reflect a maternal immune response against fetal antigens (Redline & Patterson 1993). In a recent study of 21 IUGR placentae with chronic villitis, 57% had associated uteroplacental vascular pathology and 52% had fetoplacental vascular pathology (Salafia et al 1996). Isolated villitis was not seen. It has been speculated that chronic villitis may be an intermediate step between a pathological process originating in the uteroplacental vessels and extending to the fetoplacental vessels (Salafia et al 1996). Further research will be necessary to confirm or refute this speculation.

1.3.4 Umbilical-Placental Blood Flow In SGA Pregnancies

Histological studies of the placentae in SGA pregnancies with abnormal umbilical artery Doppler waveforms have consistently shown pathological changes in the placental vessels and/or in the tertiary stem villi. These studies are considered in detail in chapter 2 of this thesis. SGA fetuses with abnormal umbilical artery Doppler studies have increased placental vascular impedance (Maulik 1995). The documented structural changes in the placental vasculature contribute to the increased impedance however altered vascular tone could also be important.

In vitro studies have shown that umbilical-placental blood flow can be modified by a number of vasoconstrictor and vasodilator substances produced in the placenta and umbilical vessels. There is conflicting evidence as to whether prostanoid production is abnormal in pregnancies with IUGR. The ratio of prostacyclin to thromboxane may have a role in the regulation of umbilical placental blood flow (Ylikorkala et al 1985). Reduced prostacyclin production from umbilical arteries in vitro (Stuart et al 1982)

and from cultured placental cells (Jogee et al 1983) have both been documented in IUGR pregnancies. Another study has reported evidence of increased reactivity of the platelet thromboxane pathway in pregnancies with IUGR (Wallenburg et al 1982). These studies published in the 1980s, stimulated the hypothesis that low dose aspirin (which inhibits thromboxane production, and alters the ratio of prostacyclin to thromboxane) might have a therapeutic role in the treatment of IUGR pregnancies (see chapter 5).

A more recent study, using small pieces of perfused placentae reported that thromboxane production, per unit of placental tissue, was not increased in IUGR pregnancies. The ratio of thromboxane to prostacyclin was also not increased, per unit of placental tissue, in IUGR pregnancies compared to controls (Sorem & Siler-Khodr 1995).

The potent and long acting vasoconstrictor endothelin-1 (ET-1) is released by endothelial cells in response to hypoxia (Rakugi et al 1990). Infusion of ET-1 into isolated perfused human placentae results in increased perfusion pressure and decreased flow (Myatt et al 1991). Raised levels of ET-1 and 2 have been demonstrated in cord blood in two small studies of pregnancies with IUGR (McQueen et al 1993, Schiff et al 1994). The highest endothelin levels in these studies occurred in IUGR fetuses with abnormal umbilical artery Doppler waveforms. More recently, in a larger study, significantly elevated ET-1 and 2 levels were again found in IUGR pregnancies with abnormal umbilical artery Doppler waveforms. No significant differences in ET-1 or 2 concentrations were found between SGA with normal Doppler waveforms and AGA controls (Harvey-Wilkes et al 1996). The endothelins

could therefore be involved in the pathogenesis of abnormal placental impedance seen in SGA pregnancies with abnormal umbilical artery Doppler waveforms, however further research is necessary to elucidate this interrelationship.

Endothelial nitric oxide synthase (eNOS) stimulates production of the vasodilator nitric oxide (NO). In a study where placentae from normal and IUGR pregnancies were immunostained for eNOS, eNOS staining was absent in the terminal villous capillaries in normal pregnancies (Myatt et al 1997). However eNOS staining was intense in the endothelium of terminal villous capillaries and stem villous vessels in IUGR pregnancies (Myatt et al 1997). Increased concentration of nitrate (a breakdown product of NO) has also been found in fetal blood in IUGR pregnancies (Lyll et al 1996). The results of both of these studies (Lyll et al 1996, Myatt et al 1997) suggest that there may be a compensatory increase in NO production in IUGR pregnancies. The mechanism for this response is currently unclear. One possible explanation is that reduced diameter of villous vessels could increase sheer stress over the endothelial cells leading to increased eNOS and NO production in response to the increased impedance. Similarly raised fetal blood concentrations of the placental vasodilator ANP have been found in pregnancies with IUGR which again suggests a possible compensatory mechanism to reduced perfusion (Kingdom et al 1992).

Abnormal placental vascular structure (in the small arteries, arterioles and capillaries) is undoubtedly important in the pathogenesis of raised placental vascular impedance (see chapter 2). Further research is necessary to determine the interrelationship between the structural and functional effects (altered vascular tone). However it has

been postulated that these pathological vascular changes represent late stages in the disease process. The process may begin with endothelial damage leading to altered synthesis of vasoactive substances, which increase impedance terminating in vascular obliteration (Myatt 1992).

1.3.5 Relationship Between Uteroplacental And Umbilical Placental

Circulations

It was stated in 1978 that 'less is known about the regulation of the placental blood flows than the regulation of blood flow to any other organ' (Rankin and McLaughlin 1979). Understanding has not advanced a lot in the intervening 20 years. There is now evidence from animal studies and from human Doppler studies that abnormal uteroplacental perfusion can result in a secondary reduction in umbilical blood flow. In a study of 10 pregnant ewes microsphere embolisation of the maternal uterine circulation resulted in subsequent increase in umbilical vascular resistance in all animals. In the seven that became growth restricted a persistent reduction in umbilical blood flow occurred (Clapp et al 1980). Longitudinal studies in high risk pregnancies have reported that abnormal perfusion in the uterine circulation (as reflected by abnormal uterine artery Doppler studies) can antedate the appearance of abnormal umbilical artery Doppler studies (Cohen-Overbeek et al 1985).

It has been hypothesised that the uteroplacental and umbilical placental circulations are matched analogous to the ventilation-perfusion matching in the lung (Rankin & McLaughlin 1979). Recently extravascular myofibroblasts have been described in placental stem villi (Demir et al 1992). These cells may have a role in the balancing of the uteroplacental and fetoplacental circulations (Benirschke & Kaufmann 1995).

The myofibroblasts are aligned longitudinally within the stem villi and it has been proposed that they may play a role in the regulation of maternal blood flow through the intervillous space (Benirschke & Kaufmann 1995). As most of the larger stem villi are anchoring villi, longitudinal contraction of myoepithelial cells would decrease intervillous volume and increase uteroplacental impedance to flow. Relaxation of the myoepithelial cells would have the opposite effect. Further research is necessary to determine the precise role of these placental myoepithelial cells and the factors which regulate them.

Rankin & McLaughlin (1979) hypothesised that matching of the placental circulations is mediated via vasoactive substances (possibly prostaglandins). This theory has been revisited more recently (Howard 1987). Howard hypothesised that reduced uteroplacental blood supply induces a reversible hypoxic vasoconstriction in the placental circulation in order to divert blood to better perfused parts of the placenta. He also proposed that if uteroplacental underperfusion was widespread this would result in hypoxia and vasoconstriction throughout the placenta. In order for the fetus to survive, humoral modulators might be produced by the fetus to reduce the vasoconstriction. If uteroplacental ischaemia was long standing this could result in irreversible fetal vasoconstriction.

Howard's theory is consistent with some of the data summarised in the preceding sections of this thesis. In vitro studies have demonstrated that an acute reduction in oxygen tension in the maternal perfusate, of a human perfused placental model, induced prompt fetoplacental vasoconstriction (Howard et al 1985). Vasoconstriction was reversed on restoration of oxygen to the perfusate. The vasoconstrictor ET-1 is

produced in response to hypoxia, is found in higher levels in cord blood from IUGR pregnancies with abnormal umbilical artery Doppler waveforms and could possibly modulate the effects of hypoxia. eNOS expression is greater and NO metabolite levels are higher in IUGR pregnancies providing evidence of a possible vasodilatory compensatory mechanism to reduced flow. The possible role of the myoepithelial cell in this process and the factors responsible for its contraction and relaxation require further research.

1.3.6 Endocrine Regulation Of Fetal Growth In SGA Pregnancies

a) Insulin like growth factors

Fetal

Transgenic mice with a homozygous deletion of the IGF-I gene have profound fetal growth failure with a birthweight approximately 60% of normal (Baker et al 1993). Postnatal growth was also impaired, confirming that growth hormone action postnatally (in the mouse) is dependent on IGF-I (Baker et al 1993). More recently the clinical details of a boy with a homozygous deletion of the IGF-I gene have been described (Woods et al 1996). This boy had profound prenatal growth restriction (birthweight about 30% of normal) as well as marked impairment of postnatal growth. This report provides direct evidence that IGF-I plays a critical role in human fetal growth as well as in postnatal growth.

Several studies have shown a correlation between levels of IGF-I in cord serum and birthweight and gestation at delivery (Verhaeghe et al 1993, Leger et al 1996, Osorio et al 1996).

A number of studies have reported IGF-I levels in cord serum of babies with IUGR. Most have found lower IGF-I levels in IUGR babies compared with appropriately grown babies (Foley et al 1980, Thierot-Prevost et al 1985, Verhaeghe et al 1993, Giudice et al 1995, Leger et al 1996). In the largest (n=254 term SGA babies) and most recent study (Leger et al 1996), lower serum IGF-I levels were found in SGA babies [32 (21) ng/ml in SGA versus 85 (36) in AGA $p < 0.001$]. Lower IGF-I levels were found in the SGA infants with low ponderal indices suggesting that intrauterine nutrition might influence the level of IGF-I. In this study wide individual variability was observed in the IGF-I levels in both normal and SGA neonates. This variability may explain why two small studies (n < 20 SGA babies) did not find a difference in IGF-I levels between SGA and AGA babies (Samaan et al 1987, Wang et al 1991).

IGFBPs modulate the actions of IGFs and transport IGFs into their target cells. High levels of IGFBP-1 have been found in amniotic fluid at 15-16 weeks gestation, in pregnancies which subsequently developed IUGR (Hakala et al 1993). Cord serum levels of IGFBP-1 have been consistently found to be inversely proportional to birthweight (Wang et al 1991, Giudice et al 1995, Osorio et al 1996, Holmes et al 1997). Elevated levels have been found in fetal blood samples (Holmes et al 1996) and cord serum at birth (Chard 1994, Osorio et al 1996) in IUGR babies. High levels of IGFBP-1 may inhibit the transfer of IGF-I into fetal tissues (Giudice et al 1995). IGFBP-1 has therefore been claimed to be an important regulator of fetal growth (Hills & Chard 1995) and appears to be a sensitive indicator of fetal nutrition (Styne 1998).

Most circulating IGF is bound to IGFBP-3 and increasing levels have been found with advancing gestation. Both decreased (Giudice et al 1995 n=10 IUGR babies, Leger et al 1996 n=254 IUGR babies) and increased (Holmes et al 1996 n=20 IUGR babies) levels of IGFBP-3 have been reported in cord serum in IUGR pregnancies. The IGFBP-3 levels were depicted graphically in IUGR babies in the report by Leger et al (1996). A large spread of results is apparent which may help explain why results differ between studies.

Maternal

In pregnancies resulting in the delivery of an IUGR baby (birthweight <5th% and abnormal umbilical artery Doppler studies), maternal serum levels of IGF-I were low compared to levels in mothers with AGA babies (Holmes et al 1998).

Maternal IGFBP-1 also correlates inversely with birthweight and high maternal serum levels were found in pregnancies with IUGR babies (Holmes et al 1997). Elevated maternal serum levels of IGFBP-1 have been reported in the second trimester (Baldwin et al 1993, Bewley et al 1993) in pregnancies which subsequently delivered growth restricted babies.

IGF and IGFBP-1 are made by the decidua. IGF-I has a mitogenic effect on endometrial cells in vitro and this effect is inhibited by IGFBP-1 (Frost et al 1993). It is thought that IGF-I is involved in trophoblast invasion of the maternal decidual and myometrial spiral arteries and that IGFBP-1 may limit IGF-I mediated trophoblast invasion (Pekonen et al 1988). It is postulated that the high levels of maternal IGFBP-1 reported in the mid trimester in IUGR pregnancies may reflect

overproduction by decidual cells. This may contribute to the defective trophoblast replacement which is often associated with IUGR pregnancies (Chard 1994). If this hypothesis is confirmed, decidual IGFBP-1 may be a maternal regulator of fetal growth.

b) Other hormones and growth factors

Reduced concentrations of placental growth hormone, as well as maternal IGF-I, have been found in the sera of pregnant women delivering IUGR babies (Mirlesse et al 1993). It is postulated, but not proven, that maternal IGF-I production is regulated by placental growth hormone (Holmes et al 1998). If this is so, placental growth hormone may be a signal by which the fetoplacental unit communicates with the mother to ensure that nutrient transfer matches fetal need. An alternative explanation is that low levels of placental growth hormone and IGF-I may result from abnormal placental development (Holmes et al 1998).

In a large study (n=254 IUGR babies Leger et al 1996), cord serum pituitary growth hormone levels were higher in IUGR babies. Similar results have been obtained by others (Deiber et al 1989, De Zegher et al 1996).

Studies in sheep have shown that a marked decrease in maternal food intake for a 20 day period resulted in increased fetal and maternal growth hormone. There was a corresponding decrease in fetal and maternal IGF-I and insulin (Bauer et al 1995). These results demonstrate that the maternal and fetal somatotrophic axes respond similarly to under nutrition. The fetal somatotrophic axis may have a role in the distribution of limited substrate supply in fetal life (Bauer et al 1998).

Pancreatic agenesis results in severe IUGR and insulin receptor abnormalities are associated with severe Dwarfism (Gluckman 1995). The effects of insulin deficiency are due to reduced cellular uptake of nutrients and reduced IGF-I production (Fowden 1995).

Purified placental microvilli from infants with IUGR have been reported to have reduced EGF receptor activity (Evain-Brion et al 1994). This reduced activity may contribute to the reduced placental size seen in pregnancies with IUGR.

Summary

IGFs are difficult to measure and results from some studies in pregnancy have been conflicting. However there is good evidence that both the IGFs and their binding proteins are important in the regulation of normal fetal growth. Animal and human studies have also demonstrated abnormal levels of IGFs and/or their binding proteins in IUGR pregnancies which suggests that they are intimately involved in the pathophysiology of this condition. Insulin, human growth hormone and placental growth hormone modulate the action of IGFs and also have a role in the regulation of fetal growth in normal and abnormal pregnancy.

Other hormones and growth factors also influence fetal growth. The relative importance and interrelationships between these agents is still largely unknown but is the focus of considerable ongoing research.

1.4 DETECTION OF THE SGA FETUS BEFORE BIRTH

Using routine abdominal palpation only 50% or fewer SGA fetuses are detected before birth (Rosenberg et al 1982, Hepburn et al 1986). Most studies have found that measurement of symphysis-fundal height is a better screening method for detection of SGA than abdominal palpation. Studies evaluating symphysis-fundal height measurement in low risk populations have reported sensitivities from 56% to 86%, specificities 73% to 89%, positive predictive values from 22% to 79% and negative predictive values from 87% to 98% for detection of SGA (Belizan et al 1978, Rosenberg et al 1982, Calvert et al 1982, Pearce and Campbell 1987, Mathai et al 1987, Harding et al 1995). Two studies of symphysis-fundal height measurement for detection of SGA in high risk pregnancies report somewhat better test characteristics (sensitivity 73%, 78%, specificity 79%, 88%, positive predictive value 60%, 70% and negative predictive value 87% and 90% respectively) (Quaranta et al 1981, Mathai et al 1987). When the utility of measuring and recording symphysis-fundal height was tested in a randomised controlled trial in a low risk population (n=1639) the prediction of SGA in the symphysis-fundal height group was not better than in the control group (Lindhard et al 1990). The detection rate for SGA in the symphysis-fundal height arm of this sole randomised controlled trial was unexplainably lower (sensitivity 28%) than had been reported in previous observational studies. Further trials are therefore necessary. In the Cochrane systematic review of symphysis-fundal height measurement it is recommended that 'it would seem unwise to abandon the use of symphysis-fundal height measurement unless a much larger trial likewise suggests that it is unhelpful' (Neilson 1997).

Computer generated growth curves, customised to an individual woman's height, weight, parity, ethnicity, and smoking status have been produced for fundal height measurement and estimation of expected fetal weight, in the second half of pregnancy. These growth curves have been evaluated as a screening method for fetal growth problems during pregnancy (Gardosi et al 1995). If fundal height measurements deviated from what was expected for that woman, a scan was performed. Introduction of these customised curves in a community setting increased the detection of SGA from 29% to 48% without increasing the number of ultrasound scans (Gardosi 1997). Further evaluation of this methodology is required to determine whether there are significant advantages, and if so, whether the benefits outweigh the cost and complexity.

Ultrasound is the best method of detecting the SGA fetus before birth and in developed countries its use is often recommended when the symphysis-fundal height is abnormal or the pregnancy has risk factors associated with an increased likelihood of an SGA baby (Harding et al 1995, Gardosi 1997). The abdominal circumference is considered an important measure of fetal growth (Campbell 1977). Liver size and the amount of subcutaneous fat both contribute to abdominal circumference measurements and both can be reduced in the undernourished fetus (Naeye et al 1965, Sumner et al 1990).

Serial ultrasound measurements are necessary to assess growth rather than a single measurement of size (Altman & Hytten 1989). Abdominal circumference along with estimated fetal weight (derived from a mathematical formula computed from ultrasound measurements including abdominal circumference) are considered the

best ultrasound predictors of the SGA fetus (Chang et al 1992, Harding et al 1995). Detection rates of 70 to 80% and positive predictive values of >60% have been reported in studies of high risk populations (Peterson et al 1989, Chang et al 1993). Similarly, serial measurements of abdominal circumference and estimated fetal weight are the best predictors of the malnourished baby, as assessed by a low newborn ponderal index of reduced skin fold thickness (Chang et al 1993).

Aiming to improve detection of fetuses which are growth restricted (and hence likely to experience morbidity), investigators have recently developed curves of fetal growth velocity obtained from serial scan measurements in normal pregnancy (Owen et al 1996). In this study at least seven scans were performed between 20 weeks and term. The expected weekly rate of increase in various fetal measurements (biparietal diameter, abdominal area, femur length and weight) was displayed graphically. These growth velocity charts were then applied to a low risk population. The aim was to predict growth restriction as assessed by skin fold thickness and ponderal index at birth (Owen et al 1998). Fetal abdominal area velocity predicted growth restriction with a likelihood ratio of 10.4 for skinfold thickness and 9.5 for ponderal index. When a likelihood ratio is >10 the diagnostic test is described as good (Jaeschke et al 1994). Therefore fetal abdominal area velocity was found to be a good method of detecting the undernourished fetus in this low risk setting. The authors did not comment on whether it was reasonable to expose these low risk women to seven scans. They also provided no data on how clinical assessment compared with growth velocity measurements in the prediction of growth restriction. Comparisons were also not made with abdominal circumference measurements. Further studies in low risk populations will be needed to confirm the utility of growth

velocity curves and to compare this methodology with measurement of abdominal circumference. This methodology has not been reported for the detection of growth restricted fetuses in a high risk setting. Evaluation in this context is also required.

1.5 COMPLICATIONS OF SGA

1.5.1 In Fetal Life And The Newborn Period

Many studies have reported that SGA fetuses are more likely to be stillborn than babies with normal birthweight for gestational age (Gardosi et al 1998, Seeds & Pena 1998, Cnattinguis et al 1998). The main reasons for the increased stillbirth rate are congenital abnormalities, chromosomal abnormalities, deaths due to hypoxia and unexplained stillbirths (Gruenwald 1963). In a review of 165 perinatal deaths at National Women's Hospital, in 1996, 20% of cases had a birthweight <10th percentile compared to 8% of total births ($p < 0.0001$) (National Women's Hospital Annual Report 1996). A recent review of third trimester stillbirths in the Trent region (Gardosi et al 1998) found that 41% of all stillbirths (after exclusion of congenital abnormalities) were small for gestational age (birthweight <10% percentile). Preterm stillbirths were more likely to be SGA than term stillbirths (53% versus 26%). There are also data which suggest that the risk of fetal death increases as the birthweight percentile decreases (Seeds and Pena 1998). Odds ratios (95% CI) for the risk of stillbirth were 2.8 (2.1-3.6) for birthweight between the 5th and 10th percentile and 5.6 (4.6-6.9) for birthweight <5th percentile compared with babies with birthweight >25th percentile. In this study babies with congenital abnormalities were excluded. A recent large Swedish study (Cnattinguis et al 1998) assessed the risk of fetal death in relation to smallness for gestational age in a population of more than a million births. Babies with congenital abnormalities were excluded. Size at birth was

assessed by calculating a birthweight ratio (actual birthweight/expected birthweight for gestation corrected for sex). Fetuses with mild SGA (birthweight ratio between 0.90 and 0.75) had an odds ratio of 2.3 (95% CI 2.1-2.5) for fetal death and those with severe SGA (birthweight ratio <0.75) had an odds ratio for fetal death of 16.5 (95% CI 15.2-17.9).

SGA babies are more likely to be hypoxic and acidotic in the antenatal period (Soothill et al 1987) and at birth, than AGA babies (Snijders et al 1993). SGA fetuses are also more likely to have abnormal fetal heart rate patterns in the antenatal period, especially in labour, (Kramer et al 1990) and to require delivery for 'fetal distress'.

Having survived the antenatal period the risk is not over. Not surprisingly, SGA babies are at increased risk of morbidity and death in the neonatal period. After birth the increased risks include polycythemia, hypoglycemia, hypocalcaemia, hypothermia, depression at birth and low apgar scores when compared with AGA babies (Kramer et al 1990). The further the birthweight centile is below the mean the greater the neonatal morbidity (Kramer et al 1990). Term SGA infants (birthweight <10th percentile) who are malnourished (ponderal index <10th percentile) are more likely to require admission to the newborn unit and to experience hypoglycemia and/or polycythemia than SGA babies with normal ponderal indices (Walther & Ramaekers 1982, Vik et al 1997). Term SGA babies with low ponderal indices spend longer in hospital and are more likely to have meconium aspiration syndrome than those with normal ponderal indices (Villar et al 1990).

Koops et al (1982) reported the risk of neonatal mortality in relation to weight for gestational age in a population of over 14,000 livebirths. At all gestations studied (24 to 42 weeks) neonatal mortality was higher in SGA than AGA babies. Babies with congenital abnormalities were not excluded in this study and they are likely to be over represented in the SGA group.

Recently Ashworth (1998) reported on birthweight-specific mortality calculated from a combination of eight data sets from developed countries. For term infants weighing 2000 to 2499 g at birth the risk of neonatal death was four times higher than for infants weighing 2500 to 2999 g and ten times higher than for infants weighing 3000 to 3499 g. However some of the data sets were from the 1970s and outcomes for term SGA infants would be expected to be better in the 1990s.

1.5.2 Complications Of SGA In Childhood

Post neonatal mortality is also increased in SGA infants. In a review article by Ashworth (1998) where the results of eight studies were combined, the overall risk of postneonatal mortality for SGA infants born at term was found to be two to four fold increased. A recent publication (Kok et al 1998) assessed long term outcome in very preterm infants (birthweight <32 weeks) in relation to weight for gestational age. SGA babies had higher mortalities in the newborn period (OR 2.6 95% CI 1.3-5.3) and in the first five years of life (OR 2.4 95% CI 1.3-4.6) after adjustment for gestational age, sex, multiple pregnancy and mode of delivery.

a) *Growth*

The majority of SGA babies experience rapid catch up growth within the first few months after birth. Most will have weight, length and head circumference measurements within the normal range for age by six months (Fitzhardinge et al 1989, Albertsson-Wikland & Karlberg 1997). However between eight and 30% will be short when measured between 18 months and four years of age (Tenovuo et al 1987, Albertsson-Wikland et al 1993, Leger et al 1997).

Most of the children who are under weight or short at six months of age will still be underweight or short at two years (Fitzhardinge et al 1989, Albertsson-Wikland & Karlberg 1997, Leger et al 1997). Children who remain small may experience more adverse social and psychological effects (Law 1987) and are more likely to have low neurodevelopmental scores (Fancourt et al 1976).

The factors which affect postnatal catch up growth are not well understood. What is currently known about perinatal variables and their influence on postnatal growth is presented in chapter 3 of this thesis.

b) *Neurodevelopment*

General

There are many studies of long term neurodevelopment in SGA children. Most studies report results from groups of SGA children born in the 1960s and 1970s where care in pregnancy, and especially in the neonatal period, was different to that in the 1990s. The results of these studies have often been conflicting. There are many reasons for the varying results including: the use of the term low birthweight

without further classification into preterm or SGA; differing definitions of SGA; inclusion of children with congenital malformations and infections, who are known to have poorer outcomes; and controls not matched for gestation. In addition, SGA babies are more likely to be born to families from socially disadvantaged backgrounds (Low et al 1978, Kramer 1998). Social disadvantage is associated with poorer cognitive outcomes and few studies have examined in detail the possible interaction between social background and birth weight (Grantham-McGregor 1998).

Furthermore, one study has reported that being SGA has a more noticeable effect on development and performance as the child ages (Low et al 1992). One other longitudinal series has reported changing neurodevelopmental status with time (Gorman & Pollitt 1992). Significant differences in neurodevelopmental scores between AGA and SGA were not identified in the first 15 months. The performance of SGA children was significantly worse in verbal and short term memory tests at 36 months. In this study, although followup was continued to five years of age, less than half the sample was tested at five years. No difference was detected between SGA and AGA at five years in this study however this could be due to insufficient power. Further adequately powered longitudinal studies of neurodevelopmental outcome in SGA children are necessary to enable more complete understanding of changes which may occur with time in these children (Grantham-McGregor 1998).

Neurodevelopment in term SGA

The literature on this subject has been reviewed by Grantham-McGregor (1998). Five studies were identified which examined term SGA children between one and two years of age (Low et al 1978, Villar et al 1984, Tenovuo et al 1988, Nelson et al

1996, Grantham-McGregor et al 1998). Lower developmental scores and more abnormal test results were found in the SGA children. These problems were particularly identified in certain subgroups, e.g male and black children (Nelson et al 1996), children with perinatal asphyxia and congenital abnormalities (Tenovuo et al 1988), those with the lowest birthweights (Low et al 1978), those with normal ponderal indices (Villar et al 1984), and those with low family income, poor housing and education (Grantham-McGregor et al 1998²). An additional study comparing development at 12 months in SGA and AGA controls found no difference in overall mental or motor development index scores but SGA had significantly lower behavioural rating scores (Pryor 1992).

A number of studies have investigated developmental outcome in SGA children born at term, aged between two and seven years (Walther & Ramaekers 1982, Villar et al 1984, Hadders-Algra et al 1988, Pryor 1992, Goman & Pollitt 1992, Goldenberg et al 1996). SGA children were more likely to have lower developmental scores and experienced more reading difficulties and poorer language development. In three studies with small sample sizes, the differences in neurodevelopmental testing between SGA and AGA were not significant (Babson & Kangas 1969, Fancourt et al 1976, Harvey et al 1982). In two studies significant cognitive differences were found between the whole SGA group and normal weight controls (Pryor 1992, Goldenberg et al 1996) but in others differences were only found in subgroups, e.g those with the earliest slowing of fetal head growth (Fancourt et al 1976, Harvey et al 1982).

Neurodevelopment in preterm SGA

Studies of neurodevelopment in preterm SGA children have also shown conflicting results and are affected by the same methodological problems as studies in term SGA children. Earlier studies in preterm SGA infants used AGA infants of similar birthweights as controls. The controls were therefore less mature and were sometimes found to have poorer outcomes than the SGA babies (Hack & Fanaroff 1984). More recent studies have used AGA controls matched for gestation and in most studies SGA children have been found to have more neurological abnormalities (Pena et al 1988, Wallace & McCarton 1997, Kok et al 1998) and lower cognitive scores (Sung et al 1993).

Summary

The evidence from the best studies of term and preterm SGA infants therefore suggests that cognitive performance is poorer in SGA infants when compared with gestation matched AGA infants. Differences between AGA and SGA may become more apparent as the child ages but further longitudinal studies of children born in the 1990s are necessary. The influence of perinatal variables on neurodevelopment in SGA infants is discussed in chapter 3 of this thesis.

1.5.3 Complications Of SGA In Adult Life

Over 40 epidemiological studies published from the late 1980s onwards have found that people who were small at birth are at increased risk of cardiovascular diseases and non-insulin dependent diabetes in later life. Most of these publications have originated from Professor Barker's group in Southampton, who were the first to report this association (Barker & Osmond 1986). The publications can be divided into four

main groups; those relating to hypertension; to insulin resistance and non-insulin dependent diabetes (NIDDM); to abnormal lipid and fibrinogen metabolism; and to coronary heart disease and stroke.

a) Size at birth and blood pressure

The association between birthweight and later blood pressure has recently been extensively reviewed by Law and Shiell (1996). They collated the results from 34 studies, from many countries, based on more than 66,000 individuals aged 0 to 71 years. The results from these studies indicate an overall inverse relationship between blood pressure and birthweight in prepubertal children and adults. During adolescence the relationship is inconsistent indicating that tracking of blood pressure may be affected by the adolescent growth spurt. The highest systolic blood pressures were seen in those with low birth weight who were obese as adults (Law et al 1993).

Some studies have found that blood pressure was inversely related to birth weight and also positively associated with placental weight (Barker et al 1990, Moore et al 1990). Other studies have not been able to confirm a relationship with placental weight (Koupilova et al 1997, Blake et al 1998).

Several recent studies have not been able to confirm an inverse relationship between birthweight and blood pressure (Whincup et al 1992, Launer et al 1993, Matthes et al 1994) and one study showed a weak positive relationship (Seidman et al 1991).

The mechanism linking reduced fetal growth with possible later hypertension is not established. It is speculated that a permanent alteration in the function of the hypothalamic-pituitary adrenal axis may be involved. Elevated levels of glucocorticoids (in Cushing's Syndrome or during pharmacological treatment) can cause hypertension (Whitworth et al 1995) and glucose intolerance (Pang et al 1992). It is speculated that the increased cortisol release which occurs in the SGA fetus (Economides et al 1988) may programme the fetus to subsequent hypertension and glucose intolerance (Newnham 1998). Others have suggested possible additional or alternative mechanisms, namely that the increase in peripheral resistance which can occur in SGA fetuses may alter the structure and compliance of vessel walls (Law et al 1993) or that abnormal renal nephron development may have a role in later hypertension (Hinchliffe et al 1992).

b) Insulin resistance and NIDDM

Low birthweight and thinness at birth (determined by a low ponderal index) have been associated with resistance to insulin and NIDDM (Hales et al 1991, Lithell et al 1996). These associations are strengthened by adjustments for current body mass index, with more obese subjects having a greater risk of insulin resistance. Evidence of insulin resistance in childhood has been found in short prepubertal children who were SGA at birth, compared with short prepubertal children who were AGA at birth (Hofman et al 1997). Other investigators have not found a relationship between birthweight and insulin secretion (Alvarsson et al 1994) or between birthweight & NIDDM (Cook et al 1993, Lawler-Heavner et al 1994)

Thin newborns lack skeletal muscle as well as fat. Insulin has an important role in stimulating cell division in fetal life, and one of its main sites of action is in muscle. It is speculated that in mid to late pregnancy the thin neonate becomes undernourished. It has been proposed that to protect essential organ growth (e.g. brain), muscles become resistant to insulin and muscle growth is reduced (Barker 1997). Some supportive evidence for this theory is that adults who were thin at birth have reduced rates of glycolysis in their muscles (Taylor et al 1995).

c) Lipid metabolism and blood clotting

Neonates with short body length in relation to head size have been found to have altered cholesterol metabolism and blood coagulation in adult life (Barker et al 1995). In this Sheffield study (Barker et al 1995) newborn abdominal circumference (reflecting liver size and subcutaneous fat) was also measured. A reduction of abdominal circumference predicted raised serum low density lipoprotein cholesterol and plasma fibrinogen levels in the adults.

d) Coronary heart disease

Hypertension, insulin resistance and disordered lipoprotein metabolism are all individual risk factors for coronary heart disease. They can also coexist in what is known as the insulin resistance syndrome or Syndrome X (Barker et al 1993¹). Coronary heart disease has been reported to be more common in people who were small at birth. In a study of 16,000 men and women born in Hertfordshire, England, between 1911 and 1930, death rates from coronary heart disease were double in individuals at the lower end of the birthweight distribution (Barker et al 1989). Data from the Sheffield study (Barker et al 1993²) also showed an increased risk of

coronary heart disease with low birthweight. In addition it was demonstrated that the increased risk was in those who were growth restricted rather than preterm. Both of these studies reported an increased risk of cerebrovascular accident with low birthweight. Association between low birthweight and coronary heart disease has been found in women, (Rich-Edwards et al 1997) and in a population from India (Stein et al 1996). The effect is independent of influences on adult lifestyle. The relationship has been found over a range of social classes and at each level of cigarette smoking and obesity.

This finding of increased coronary heart disease in individuals of low birthweight, has led to the hypothesis that coronary heart disease is programmed by under nutrition in utero (Barker 1995). The basis for this hypothesis is that in fetal life various organs go through so called critical periods of development (Widdowson and McCance 1975) which can coincide with times of rapid cell division. When the fetus is faced with an under supply of oxygen or nutrients it can respond by slowing its rate of cell division, especially in tissues which are rapidly dividing. It is thought that under nutrition even for a short time, may reduce cell numbers in particular organs (Widdowson & McCance 1975) hence resulting in a permanent change or programming in the body. There is considerable evidence from many epidemiological studies, from animal experiments and from some clinical studies to support this hypothesis. Many groups around the world are now conducting experiments to elucidate the possible mechanisms underlying these epidemiological associations. If a cause and effect relationship between SGA and cardiovascular disease is confirmed, then understanding the mechanisms involved could result in prevention strategies with enormous public health implications.

The fetal hypothesis outlined above has not met with universal support (Joseph & Kramer 1996, Rasmussen 1998). Criticisms of the original epidemiologic studies have been raised (Joseph & Kramer 1996). It is claimed that selection bias may have influenced the results of the numerous studies conducted in the Hertfordshire area. Of 15,600 eligible male subjects, only 5,700 were available for analysis in the original publication on birthweight and coronary heart disease (Barker et al 1989). Even smaller numbers of the eligible Hertfordshire subjects were assessed for some of the other studies e.g impaired glucose tolerance study, n=370, (Hales et al 1991), fibrinogen study, n=591 (Barker et al 1992). It has been argued that in spite of large loss to follow up, bias would only occur if the relationship between infant weight and coronary heart disease differed in those subjects traced and those lost to follow up and that a systematic difference is unlikely (Leon 1998).

There are also concerns of residual confounding due to socioeconomic factors which effect birthweight and were not able to be adjusted for (Ben-Shlomo & Smith 1991, Joseph & Kramer 1998). Leon (1998) and Joseph & Kramer (1998) argue against a causal explanation for the observed association between birth weight and cardiovascular disease.

Alternative hypotheses have been presented. The first postulates that genetic and environmental factors may be responsible for the association between size at birth and cardiovascular disease in adulthood (Rasmussen 1998). Rasmussen contends that bigger babies come from better nourished women. The predictors of being born to a better nourished mother are also the predictors of a healthier lower stress life,

which could result in a lower rate of adult cardiovascular disease. Good fetal growth would therefore be a proxy for good socioeconomic circumstances. Rasmussen also argues that socioeconomic confounders may be important in the relationship between low birthweight and later cardiovascular diseases.

Hattersley et al (1998) have hypothesised that the same genetic influences could alter both intrauterine growth and adult glucose tolerance (thrifty genotype hypothesis). They have identified a heterozygous mutation in the glucokinase gene which results in a defect in the glucose sensing mechanism of the β -cells and also defective insulin secretion. Inheritance of the glucokinase mutation by the fetus resulted in a mean reduction in birthweight of 533 g (n=58) and was also associated with postnatal hyperglycemia. Before the thrifty genotype hypothesis can gain widespread support further studies are necessary to determine the prevalence of this and other mutations which influence insulin secretion.

1.6 MANAGEMENT OF PREGNANCIES WHERE THE FETUS IS SGA

1.6.1 General Principles

There is no consensus in the literature as to what is the most appropriate or effective management for pregnancies where the fetus is SGA. Management is influenced by a number of factors including the underlying diagnosis and the gestational age. A careful review of gestational age and ultrasound review of fetal anatomy is essential. If any markers are present, which raise the possibility of chromosomal abnormality, then cordocentesis may be considered. If a serious underlying fetal problem (congenital or chromosomal abnormality, some congenital infections) is recognised the chance of quality extrauterine survival may be poor and conservative

management may be appropriate. Underlying fetal problems are more likely when SGA is recognised in the second or early third trimester and are estimated to occur in approximately 10% of such pregnancies (Lapillonne et al 1997).

A careful maternal history and examination is necessary to exclude predisposing conditions such as maternal vascular diseases, including preeclampsia, chronic hypertension and autoimmune diseases. Maternal hypertensive disease (usually preeclampsia) is found in about 30% of cases of IUGR (Lapillonne et al 1997). In many cases no obvious underlying maternal or fetal condition is detected and the cause in the majority of such cases is thought to be 'uteroplacental dysfunction' (Kramer and Weiner 1997).

Most obstetricians recommend that SGA pregnancies require careful monitoring (de Vore 1994, Visser 1995, Kramer and Weiner 1997). This monitoring should incorporate umbilical artery Doppler assessment (where available), which has been shown to reduce perinatal mortality in high risk pregnancies with preeclampsia and/or SGA (Neilson & Alfievic 1998). Umbilical artery Doppler studies may identify genuinely compromised fetuses and assist in the optimum timing of delivery (Alfievic and Neilson 1996). A recent survey of practice of American maternal fetal medicine specialists reported that most recommend fetal surveillance and bed rest in SGA pregnancies, regardless of whether umbilical artery Doppler is normal or abnormal (de Vore 1994). It is not known whether these results reflect cautious practice, which is guided by the risk of litigation should an adverse outcome occur, or a lack of faith in umbilical artery Doppler technology. The role of Doppler in SGA pregnancies is discussed in detail in chapter 2 of this thesis. In some centres, hospitalisation for

suspected growth restriction is usual practice (Nienhuis et al 1994). A randomised trial of hospitalisation for bed rest in SGA pregnancies did not show an improvement in fetal outcomes (Laurin & Persson 1987). This study was underpowered and the method of randomisation (odd or even according to maternal birth date) was subject to bias. Further trials are necessary to confirm or refute whether bed rest is of benefit in SGA pregnancies.

Again there is no evidence that introducing a programme of regular fetal surveillance (other than umbilical artery Doppler) in SGA pregnancies improves outcome. A meta-analysis of four studies of antenatal cardiotocography conducted in high risk pregnancies in the 1970s and 1980s did not show an improvement in perinatal outcome (Neilson 1995). These trials were carried out during the infancy of fetal heart rate monitoring and in some cases clinicians were inexperienced in interpretation of fetal heart traces. A reanalysis of these data (Pattison & McCowan 1999) recommends that large new trials are necessary but acknowledges that these are unlikely to be carried out. Despite the lack of benefit from trial data, antenatal cardiotocography is still commonly performed to monitor fetal wellbeing in SGA pregnancies.

An alternative, but perhaps less widely used method of fetal assessment is the biophysical profile score (Manning et al 1980). This score has been found to correlate with fetal pH in SGA fetuses (Ribbert et al 1990). Again no substantive improvements in perinatal outcome have been demonstrated in randomised trials using this technique (Alfirevic & Neilson 1995).

1.6.2 Management Of SGA Near Term

Despite the lack of good trial data confirming or refuting the role of fetal monitoring in SGA pregnancies, it is common practice to monitor fetal health regularly, utilising the antenatal cardiotocograph or biophysical profile score. Repeat ultrasound scanning for growth at two to four weekly intervals is commonly recommended. Delivery by term would be usual with earlier delivery recommended if oligohydramnios developed (Kramer and Weiner 1997), fetal growth was static, or if there was suspicion of fetal compromise. The aim would be to deliver the fetus before it became acidotic (Visser 1995) as antenatal acidosis in babies born SGA has been associated with lower developmental quotients in early childhood (Soothill et al 1992, Soothill et al 1995).

1.6.3 Management Of SGA Remote From Term

When SGA is recognised in the second or early third trimester a careful search for fetal causes is required. If the fetus is of a viable gestation and weight (the threshold for which varies from institution to institution) increased fetal surveillance would be usual. If the fetus is likely to require delivery at <32 weeks, corticosteroids should be prescribed to enhance fetal lung maturation (Crowley 1996). Management is more difficult in the extremely preterm fetus as survival and morbidity is closely linked to the gestational age at birth. There is no good data from randomised controlled trials to guide practice. Most obstetricians recommend delaying delivery until the fetus is mature or until signs suggestive of early fetal compromise occur (Visser 1995, Newnham 1998). Again it is recommended that delivery should be timed to avoid fetal acidosis (Visser 1995). Hopefully in the near future there will be good evidence available to guide practice for the difficult clinical problem of management of the preterm SGA fetus. The Growth Restriction Intervention Trial based in Leeds,

England, is addressing this issue. In this trial if the obstetrician is unsure whether or not to deliver the SGA fetus electively, and the woman consents, randomisation is undertaken to 'deliver now' (delivery usually delayed until after administration of corticosteroids) or to 'defer delivery'. In the 'defer delivery' group it is recommended that delivery is deferred until signs of deteriorating fetal wellbeing occur or until the risks of premature delivery are less.

1.6.4 Summary

Many aspects of management of SGA pregnancy are not currently based on good evidence. Most obstetricians recommend a programme of regular fetal surveillance and aim to deliver the fetus before there is fetal acidosis.

1.7 TREATMENT FOR SGA PREGNANCIES

Most of the studies which have evaluated whether a therapeutic intervention reduces the rate of SGA (or increases birthweight) have done so in pregnancies at high risk of SGA rather than in pregnancies where the fetus is already thought to be SGA. These preventative studies can be divided into three broad groups and will be discussed only briefly as prevention of SGA was not the focus of the research presented in this thesis. The studies addressing treatment of established SGA will be covered in more detail.

1.7.1 Preventative Studies

a) Care and advice during pregnancy

Cigarette smoking is common in pregnancy and causes a dose dependent reduction in birthweight. In developed countries smoking is the most important etiological

determinant of low birthweight (Kramer 1987). The results of 40 trials (n=9000 women) of smoking cessation in pregnancy have recently been summarised in a Cochrane systematic review (Lumley et al 1998). Pregnant women were randomised to a range of interventions aimed at reducing smoking. Low birthweight was reduced in treatment groups (OR=0.80, (95% CI 0.67 to 0.97)). A greater effect was found in studies where more women stopped smoking.

The provision of additional social support to women at high risk of preterm birth or delivering a low birthweight baby has not been found to affect mean birthweight or delivery of a SGA baby (Hodnett 1997).

b) Nutritional supplementation

There are several systematic reviews of a range of nutritional supplements during pregnancy and their influence on birthweight. One of the most promising is balanced protein/energy supplementation (nutritional supplement where <25% of the total energy is made up of protein). A modest increase in maternal weight gain and fetal growth was found after systematic review of nine studies conducted in both developing and developed countries (Kramer 1997). Pre-pregnancy nutritional supplementation may be of greater benefit than treatment given only during pregnancy (Caan et al 1987, Viteri et al 1989).

Vitamin and mineral supplementation have also been studied. Low levels of zinc have been found in SGA pregnancies (Simmer & Thompson 1985) and in a systematic review of zinc supplementation in pregnancy (n=1400) a trend [OR 0.77 (95% CI 0.54-1.11)] to reduced SGA was found (Mahomed 1997). Most studies were

carried out in normal pregnancies with a low prevalence of SGA. Further studies are therefore necessary to achieve sufficient power to determine whether zinc treatment is of benefit in the prevention of SGA.

Magnesium is a cofactor for many enzymes and is necessary for protein synthesis.

The role of magnesium supplementation in pregnancy has also been assessed in a systematic review on a range of pregnancy outcomes (Makrides & Crowther 1998).

A reduced incidence of low birthweight and SGA was found in magnesium treated pregnancies but five of the six trials had methodological problems. Further well designed trials are necessary to determine whether magnesium is beneficial.

Similarly, a systematic review of routine folate supplementation in pregnancy showed a trend to a reduced incidence of low birthweight (Mahomed 1997). Again several of the trials had methodological problems and further studies are necessary. In addition, all of the folate trials were performed in populations receiving routine iron supplements.

c) Pharmacological therapy

The role of low dose aspirin in the prevention of growth restriction in high risk pregnancies has been evaluated in a number of randomised controlled trials which have been summarised in a meta-analysis published in 1997 (Leitch et al). Thirteen trials, including more than 13,000 women were included. Only two of the thirteen studies reported a significant reduction in the odds of SGA. However after meta-analysis the combined odds ratio for SGA with aspirin treatment was 0.82 (95% CI, 0.72 - 0.93). There was a trend to reduced perinatal deaths OR 0.84 (95% CI 0.66-1.08). Subgroup analysis suggested that higher doses of aspirin (100 to 150 mg/day)

were more effective for prevention of IUGR than lower doses (50-80 mg/day), OR 0.36 (95% CI 0.22-0.59) and 0.87 (95% CI 0.76-0.99), respectively. Similarly, treatment started before 17 weeks was more effective than later treatment OR 0.35 (95% CI 0.21-0.58) and 0.87 (95% CI 0.76-0.99), respectively.

Unpublished studies were not included in this meta-analysis, so there is a possibility of publication bias. Since this meta-analysis was published another large aspirin study (n=2539), in high risk women, has been published (Caritis et al 1998). Women with insulin dependent diabetes, chronic hypertension, multiple pregnancy and previous preeclampsia were randomised to low dose aspirin (60 mg) or placebo. No difference was found in rates of SGA between aspirin (10%) and placebo treated (9%) nor in rates of perinatal deaths or preeclampsia. When the results of this large study are added to the meta-analysis the possible protective effects of low dose aspirin on SGA, in the lower dose range, may be reduced or not significant.

1.7.2 Therapeutic Studies In Pregnancies With Suspected SGA

a) Hospitalisation

With the aim of maximising uteroplacental perfusion, bed rest is often recommended as therapy in SGA pregnancies. Only one randomised controlled trial (n=107) has evaluated the effect of bedrest in hospital in pregnancies with suspected IUGR (Laurin & Persson 1987). Randomisation was by odd or even maternal birth date which can be associated with selection bias. No differences were found in fetal growth parameters or other neonatal outcomes between bedrest and ambulatory groups. This study did not have sufficient power to detect a difference in birthweight between groups. At present there is no evidence to support the common practice

that bedrest promotes fetal growth, but further well designed trials are necessary (Gulmezoglu & Hofmeyr 1994).

b) Abdominal decompression

Abdominal decompression is a technique which was originally developed with the intention of relieving the pain of uterine contractions in labour (Heyns 1959). The method utilises intermittent abdominal decompression in a Heyn's plastic suit which covers a rigid frame enabling the pressure around the abdomen to be reduced. A negative pressure of 70 mmHg was applied at intervals e.g 30 seconds every minute for 30 minutes twice daily. This technique was thought to enhance uteroplacental blood flow (Heyns et al 1962). This was subsequently confirmed when a 30% increase in placental blood flow was detected using radioactive isotopes (Coxon & Haggith 1971). Three small randomised trials have been conducted to evaluate the technique as a treatment for preeclampsia or fetal growth restriction (Blecher 1967, MacRae et al 1971, Varma et al 1973). All trials had methodological problems. In the first (Blecher et al 1967) allocation to study and control groups was by alternation, observers were not blinded and outcome measures were subjective. In the second study (MacRae et al 1971) the method of selection of subjects was not described. In the third, subject allocation was changed in seven women and reanalysis by intention to treat was not possible. Again observers were not blinded and outcome measures were subjective. The meta analysis showed reduced low birthweight (RR 0.50 95% CI 0.40-0.63), faster weekly biparietal diameter growth [2.08 (0.36) versus 1.49 (0.71) mm/week] and reduced perinatal mortality (RR 0.39, 95% CI 0.22-0.71). It is recommended that the results of these trials should be interpreted with caution

because of methodological shortcomings and that further stringently designed studies are necessary (Hofmeyr 1995).

c) Oxygen therapy

Fetal growth restriction is associated with hypoxaemia, hypoglycemia and other metabolic abnormalities. Findings from uncontrolled studies utilising cordocentesis demonstrated that hypoxaemia could be improved by maternal oxygen therapy (Nicolaides et al 1987). Two randomised trials were subsequently carried out where the aim was to determine whether continuous oxygen treatment would increase fetal growth and improve perinatal outcome (Battaglia et al 1992, Johanson et al 1995). Both studies had methodological problems. In the first, the method of randomisation was not specified and it is not stated whether those assessing outcome were blinded to treatment allocation. In the second, randomisation methods were suboptimal (sealed opaque envelopes) and outcome assessments were not blinded. A meta-analysis of these studies showed that perinatal mortality was lower in the oxygen treated group RR 0.41 (95% CI 0.21 to 0.78) but there was no improvement in birthweight (Gülmezoglu & Hofmeyr 1997). The differences in mortality rates could be explained by the imbalance of gestational age in favour of the oxygen treated subjects. It is concluded that the current studies are too small to give reliable estimates of any benefits or the safety of oxygen therapy in SGA pregnancies. Maternal oxygenation for suspected impaired fetal growth should only be used in the context of well designed randomised trials (Gülmezoglu & Hofmeyr 1997).

d) *Nutritional treatment*

During the Dutch famine in 1944 to 1945 it was found that nutritional deprivation had an adverse effect on fetal growth (Smith 1947). In this period severe caloric restriction (< 1500 cal/day) in the third trimester of pregnancy was associated with a median decrease in birthweight of 240 gm. This data provided the stimulus for the first studies of nutritional supplementation in populations at high risk of IUGR. It also created interest in trials of nutritional supplementation as therapy in pregnancies with suspected IUGR. Three small randomised trials of nutrient supplementation in pregnancies with suspected impaired fetal growth (none of which are published in English) have recently been reviewed in the Cochrane Library (Gülmezoglu & Hofmeyr 1996). In the first small double blind placebo controlled study (Herre 1976) intravenous protein-free calf blood extract (Solcoseryl) was administered to the study group. Treatment was associated with improved 24 hour oestrogen secretion but the study was too small to estimate clinical outcomes. In the second small study (Genger 1988) carnitine was given orally for two weeks to 15 patients with so called 'placental insufficiency'. There was no improvement in birthweight or birthweight centiles. In the third study (Viehweg 1987) 60 women with suspected impaired fetal growth were randomised to bed rest, or intravenous glucose or oral galactose supplements. Again there was no difference in SGA between groups. It was concluded in the systematic review that there is no current evidence to recommend nutrient therapy for suspected fetal growth impairment. The trials examined were inadequate to elucidate the effectiveness of nutrient therapy and further research is necessary to evaluate the effectiveness and/or risks of nutrient therapy in suspected impaired fetal growth.

e) *Pharmacologic therapies*

Beta mimetics

Beta mimetics produce a range of systemic effects via action on adenylyl cyclase. The resultant relaxation of uterine muscle can lead to decreased resistance to uterine blood flow and increased uterine perfusion (Lippert et al 1980). This increase in perfusion may be of benefit for treatment of babies with IUGR. These agents also increase blood glucose which may enhance growth. Two randomised trials of beta mimetic treatment in IUGR have been reported (Cabero et al 1988, Mori et al 1990) and the results have been combined in a systematic review (Gülmezoglu & Hofmeyr 1997). There are methodological problems with the first study and the second is only published in abstract. Women with suspected IUGR were randomised to oral ritodrine or no treatment in the first trial and to intravenous ritodrine or no treatment in the second trial. Both studies were small and no significant improvements in birthweight were found with treatment. There is currently therefore inadequate evidence to either recommend or refute a role for beta mimetics to promote fetal growth.

Low dose aspirin

The role of low dose aspirin as a therapy for IUGR has been reported in three previous randomised placebo controlled trials (Trudinger et al 1988, CLASP 1994, Newnham et al 1995) and the current data is conflicting. In chapter 5 of this thesis the results of our randomised controlled trial of low dose aspirin for the treatment of SGA fetuses with abnormal umbilical artery Doppler is reported and a detailed review of the previous literature is presented there.

CHAPTER 2

THE DOPPLER TECHNIQUE AND DOPPLER STUDIES IN PREGNANCY

2.1 BACKGROUND AND PHYSICS

The Doppler effect is a change in frequency or wavelength due to motion. In medical applications, as first described by Satomura in 1959, it is the flow of blood which generates the Doppler effect. Technological advances have resulted in the widespread use of Doppler for clinical investigation and in 1977 Fitzgerald and Drumm were the first to report the study of the human fetal circulation using Doppler ultrasound.

When an ultrasound beam impinges upon a blood vessel the beam is scattered by the many moving red blood cells (fig 2.1). This results in a change in frequency of the ultrasound beam (Doppler shifted frequency) which is proportional to the velocity of the blood flow, as seen in the Doppler equation below.

$$\Delta f = \frac{2f_t \cdot V \cdot \cos \theta}{c}$$

Δf = Doppler shifted frequency

f_t = transmitted frequency of ultrasound

V = velocity of blood flow

$\cos \theta$ = the angle between the ultrasound beam and the direction of blood flow

c = the speed at which sound is propagated through tissue

As c and f_t are constant it can be deduced that the Doppler shifted frequency (Δf) is not only proportional to the velocity of blood flow but also to the angle between the ultrasound beam and the vessel. When $\cos \theta$ approaches 1 (angles between the ultrasound beam and vessel close to zero or 180°) the greatest Doppler shift is obtained, whereas an angle of 90° ($\cos 90^\circ = 0$) produces a negligible Doppler shift.

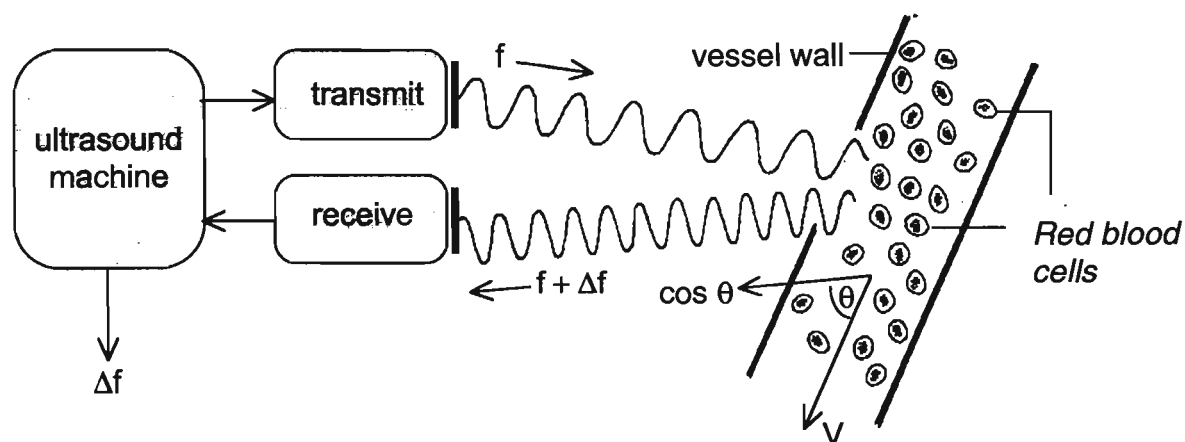


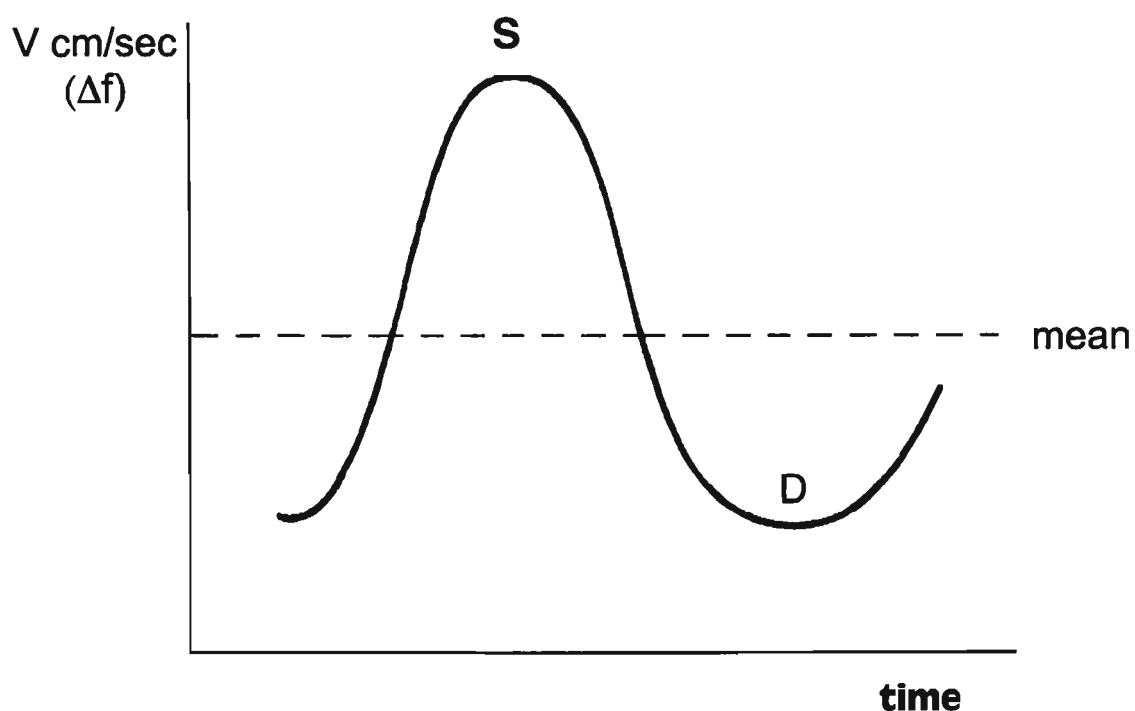
Fig 2.1 **Ultrasound beam impinging on red blood cells in a blood vessel with resultant changes in frequency**

The Doppler shifted frequencies undergo spectral analysis by the ultrasound machine and a flow velocity waveform is produced. The shape of the maximum frequency envelope of the flow velocity waveform from an arterial source is determined by upstream and downstream circulatory factors. The peak systolic frequency shift (S) is influenced by cardiac output, and vessel compliance (Skidmore & Woodcock 1980). The end-diastolic frequency shift (D) is related to vascular impedance defined as the opposition to flow in a pulsatile circulation (Maulik 1995) (fig 2.2). Impedance depends on resistance as well as other factors such as blood

viscosity. Vasodilatation results in a decrease and vasoconstriction in an increase in impedance.

The Doppler flow velocity waveforms are analysed mathematically by creating a ratio of the maximum systolic frequency shift to the end-diastolic frequency shift (fig 2.2).

The resistance index (maximum systolic Doppler shifted frequency minus end-diastolic Doppler shifted frequency divided by maximum systolic Doppler shifted frequency ($\frac{S-D}{S}$)) is used for the purposes of waveform analysis in this thesis.



$$\text{Resistance index} = \frac{S-D}{S} \quad S/D \text{ ratio} = S/D \quad \text{Pulsatility index} = \frac{S-D}{\text{mean}}$$

Fig 2.2 Maximum frequency envelope of Doppler flow velocity waveform showing peak systolic frequency shift (S) and end-diastolic frequency shift (D)

Laboratory and animal studies have shown good correlations between resistance indices and vascular resistance in the placenta (Trudinger et al 1987, Adamson et al 1990) and between resistance indices and parameters of impedance (Downing et al 1989). The methodology for obtaining Doppler studies from fetal and maternal vessels in pregnancy is described in chapter 4 (general methods).

2.2 CHANGES IN NORMAL AND PATHOLOGICAL PREGNANCIES

Previous work by our group (Duggan and McCowan 1993) and others (Trudinger et al 1985, Erskine & Ritchie 1985) has shown that as normal pregnancy advances the end-diastolic Doppler shifted frequency in the umbilical artery flow velocity waveform increases (fig 2.3) resulting in a progressive lowering of the resistance index (fig 2.4). This is consistent with a gradual decline in impedance, due to the progressive growth and dilatation of the placental arterial and capillary circulation (Maulik 1995).

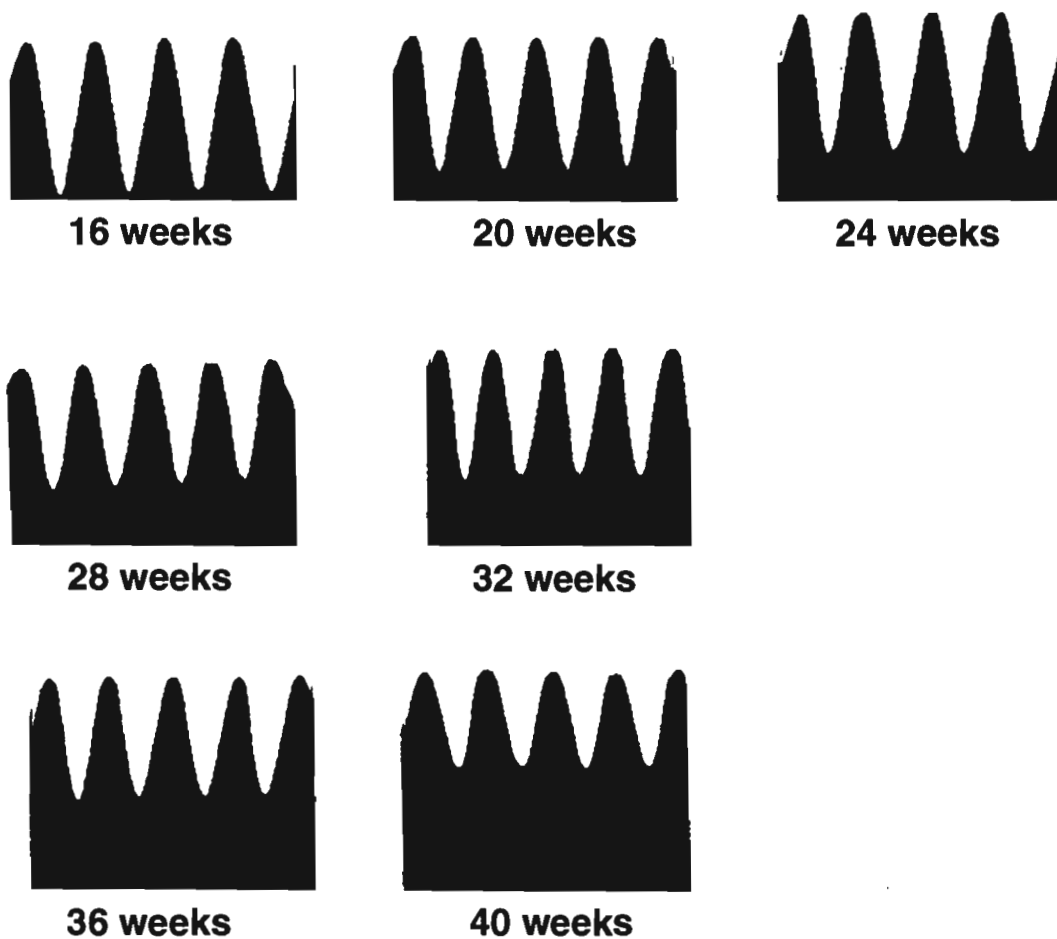


Fig 2.3 Diagrammatic representation of umbilical artery Doppler flow velocity waveforms demonstrating increase in end-diastolic frequencies as pregnancy advances

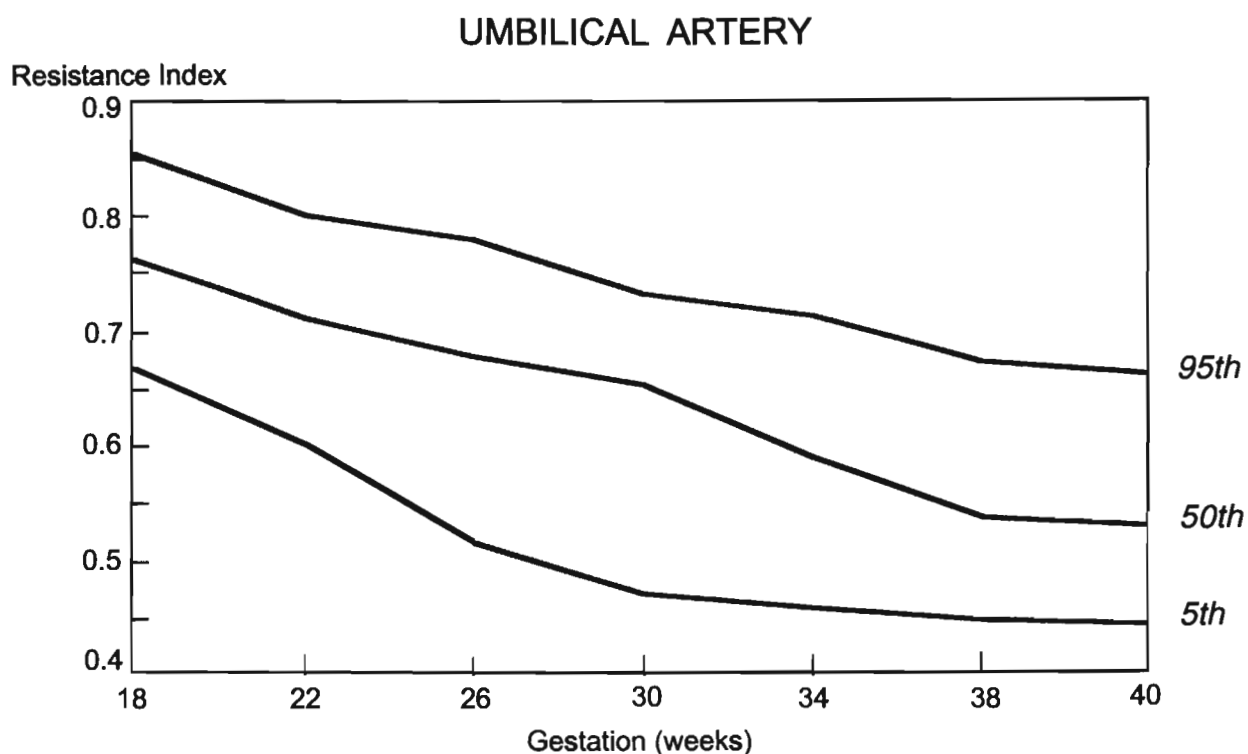


Figure 2.4 Change in resistance index with advancing gestation

(Duggan & McCowan 1993)

In some pathological pregnancies especially with SGA fetuses and/or preeclampsia this fall in umbilical arterial resistance indices with advancing gestation does not occur. This can result in Doppler waveforms with reduced, absent or even reversed end-diastolic Doppler shifted frequencies or velocities (fig 2.5) and a resistance index which is outside the normal range for pregnancy. These abnormal waveforms are thought to result from placental vascular obliteration and possibly vasoconstriction which causes arterial impedance to increase due to enhanced pressure and flow velocity wave reflections (Maulik 1995). Mathematical models of the umbilical placental circulation have been created in which the terminal branches of the arterial vascular tree in the model have been progressively obliterated to mimic placental

vascular disease (Thompson and Trudinger 1989). In this model the pulsatility index increased slowly as vessels were obliterated. A sharp increase in pulsatility index occurred when at least 60% of vessels had been obliterated. Obliteration of a given proportion of vessels had a more marked effect on the pulsatility index in small placentae, whereas in large placentae obliteration of a greater number of vessels was necessary to achieve an increase in pulsatility index. Studies in ovine models have provided support for this vascular obliteration model for the abnormal umbilical artery Doppler waveform. Embolisation of the umbilical placental circulation results in an increase in placental resistance and in umbilical artery resistance indices (Trudinger et al 1987, Adamson et al 1990). On occasion failure of normal placental vascularisation (rather than obliteration) may result in the abnormal umbilical artery Doppler waveforms, as seen in fetuses with karyotypic abnormalities (Kuhlmann et al 1990).

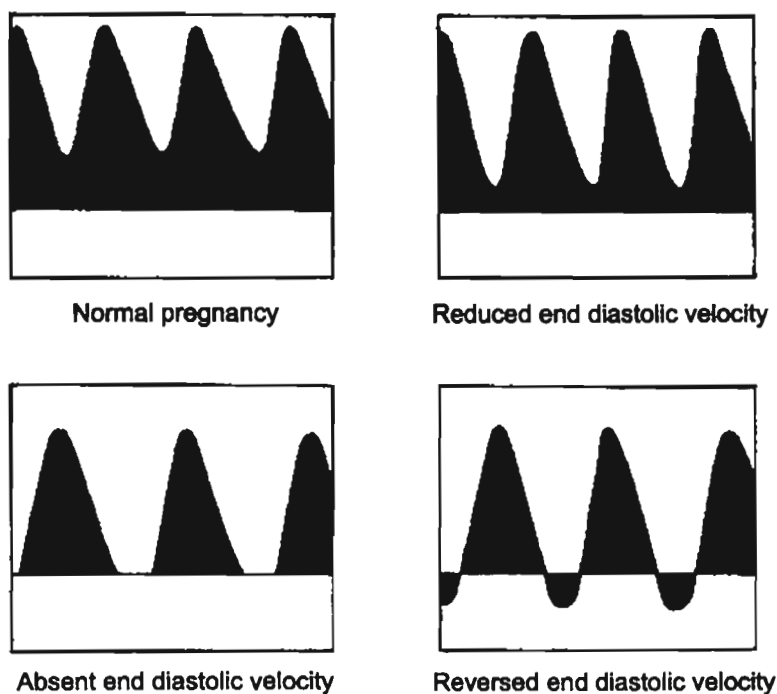


Fig 2.5 Umbilical artery flow velocity waveforms from normal and pathological pregnancies

2.3 PLACENTAL HISTOLOGY IN PREGNANCIES WITH ABNORMAL UMBILICAL ARTERY DOPPLER WAVEFORMS

A range of placental vascular and morphological abnormalities have been identified in placentae from SGA pregnancies with abnormal umbilical artery Doppler waveforms. Earlier studies (Giles et al 1985, McCowan et al 1987, Bracero et al 1989, Fok et al 1990) focussed their attention on the small placental arteries and arterioles (20-90 μg diameter) as it was thought that these vessels likely accounted for the major change in arterial blood pressure (and hence resistance) in the placenta (Walsh and Lind 1978). These four studies all found a reduction in the numbers of small placental arteries and arterioles in placentae from pregnancies with abnormal umbilical artery Doppler waveforms. It was reported that “a microvascular basis for the abnormal Doppler waveforms had been identified” (Giles et al 1985). In three of these four studies the pathologist was reported to be blinded to the Doppler results at the time of pathological assessment and in one study (Giles et al 1985) this information was not reported.

Recent reviews have studied placental morphometry and villous architecture in more detail and compared the findings in pregnancies with normal and abnormal umbilical artery Doppler studies. These studies consistently demonstrated a reduction in villous surface area in placentae from growth restricted pregnancies with abnormal umbilical artery Doppler studies (Hitschold et al 1993, Macara et al 1995, Jackson et al 1995). Additionally they also found evidence of generalised hypovascularity rather than just a selective loss of small stem vessels (Hitschold et al 1993, Macara et al 1995, Jackson et al 1995). This does not negate the findings of the four earlier studies which reported reduced numbers of small placental arteries and arterioles

(Giles et al 1985, McCowan et al 1987, Bracero et al 1989, Fok et al 1990) as larger vessels and capillaries were not counted in these studies.

Terminal villi develop in the third trimester (Kaufmann 1982). They are vascularised by branched capillaries with sinusoidal dilatations. The time course of this placental growth and vascularisation parallels the fall in placental vascular impedance which occurs in normal pregnancy as reflected by longitudinal umbilical artery Doppler studies. Abnormal development of this capillary network could therefore also result in or contribute to the high impedance circulation seen in SGA pregnancies with abnormal umbilical artery Doppler waveforms. Two studies have specifically reported on changes in the capillaries of the terminal villi in SGA pregnancies with abnormal umbilical artery Doppler waveforms (Jackson et al 1995, Krebs et al 1996). Krebs et al (1996) performed an elegant and detailed review of placental capillary architecture in SGA pregnancies. Plastic casts were obtained of placental cotyledonary vessels. SGA fetuses with absent end-diastolic velocity in the umbilical artery were found to have reduced numbers of capillary loops which were longer, less coiled and less branched than in gestation matched controls. They also found abnormalities on the trophoblast surface of the placenta, including fibrin plaques. Reductions in the number of capillaries in the terminal villi was also demonstrated by Jackson et al (1995), who, in addition, found a reduced surface area of intermediate and terminal villi.

Ultrastructural studies, using an electron microscope have revealed additional changes in the placentae of growth restricted fetuses with abnormal umbilical artery Doppler studies, compared to AGA control placentae (Macara et al 1996). In this

report the terminal villi in the IUGR placentae were found to be smaller than in the AGA placentae. Other abnormalities were also demonstrated including: increased syncytial nuclei, decreased cytotrophoblast nuclei and features which would impair placental transfer including stromal fibrosis, thickened basal lamina and capillaries congested with red blood cells.

2.3.1 Summary

Placentae from growth restricted pregnancies with abnormal umbilical artery Doppler studies have been shown to have abnormal vascularity extending from the stem villi to the terminal capillary network. These vascular abnormalities are likely responsible, at least in part, for the coexisting abnormal umbilical artery Doppler waveforms.

2.4 CLINICAL UMBILICAL ARTERY DOPPLER STUDIES

2.4.1 Non-randomised Studies

Beginning in the mid 1980s, many publications have reported the role of umbilical artery Doppler studies in normal and more particularly in abnormal pregnancies.

Umbilical artery Doppler velocimetry has been applied as a screening test in low and medium risk populations to predict later SGA (Beattie & Dornan 1989, Newnham et al 1990, Atkinson et al 1994, Todros et al 1995). In these populations the sensitivity (10%-30%) and specificity (89%-95%) are low resulting in more false positive than true positive diagnoses of SGA. Umbilical artery Doppler studies can therefore not be recommended as a screening test in low or medium risk populations (Alfirevic & Neilson 1996).

Studies in high risk populations have shown better test performance of umbilical artery Doppler studies to predict a range of adverse outcomes. Trudinger et al (1986) compared umbilical artery Doppler velocimetry with the nonstress test for predicting SGA or an apgar score <7 at 10 minutes in 170 high risk pregnant women. The two tests performed similarly. The test characteristics for umbilical artery Doppler waveform analysis were: sensitivity 60%, specificity 85%, positive predictive value 64% and negative predictive value 83%. Umbilical artery Doppler screening at 34-36 weeks gestation, in a high risk population (n=350) has been shown to perform well in the prediction of SGA and fetal or newborn morbidity (defined as abnormal intrapartum CTG, thick meconium, acidosis at birth, five minute apgar <7 and/or admission to the newborn unit). In this study the test characteristics for predicting fetal or newborn morbidity were: sensitivity 86%, specificity 88%, positive predictive

value 68% and negative predictive value 96% with a Kappa index of 0.73, indicating very good test performance (Maulik et al 1990).

A small number of non-randomised studies have assessed pregnancy outcome in SGA fetuses with normal umbilical artery Doppler studies. A low rate of pregnancy complications has been reported compared with SGA fetuses with abnormal umbilical artery Doppler studies (Reuwer et al 1987, Burke et al 1990, Trudinger et al 1991). These SGA fetuses with normal umbilical artery Doppler velocimetry are unlikely to develop signs of fetal distress before (Bekedam et al 1990) or in labour (Dempster et al 1988). They are less likely to experience morbidity in the newborn period (Trudinger et al 1991) including periventricular haemorrhage (Gaziano et al 1994) than SGA babies with abnormal umbilical artery Doppler studies. It has therefore been suggested that more conservative management with less intervention could be safely implemented in these pregnancies (Burke et al 1990, Gaziano et al 1994). To date, there has only been one trial which has addressed the issue of less intervention in SGA pregnancies with normal umbilical artery Doppler studies (Nienhuis et al 1997). This trial was conducted in a Dutch centre where hospitalisation was usual for IUGR. In women randomised to receive usual care the Doppler results were concealed (n=74). In the intervention group (n=76) it was recommended that hospitalisation should not occur if umbilical artery Doppler studies were normal. No differences were found in rates of hospitalisation or newborn morbidity between the two study groups, but this study did not have sufficient power to detect a difference. In chapter 6 of this thesis a pilot randomised controlled trial of two regimens of fetal surveillance in SGA pregnancies with normal umbilical artery

Doppler studies is presented. The aim is to determine whether the frequency of fetal surveillance can be reduced without increasing maternal or perinatal morbidity.

Some authors have also suggested that these SGA fetuses with normal umbilical artery Doppler studies are not malnourished but are normal small babies (Burke et al 1990, James et al 1992, Soothill et al 1993). There is currently no data to confirm this speculation. Data on markers of newborn nutrition in relation to umbilical artery Doppler status are presented in chapter 7 of this thesis.

Many studies have shown a link between abnormal umbilical artery Doppler results, especially absent end-diastolic velocity and a range of adverse perinatal outcomes. The adverse outcomes which have been associated with abnormal umbilical artery Doppler studies include hard outcomes such as death (Trudinger et al 1991, Valcamanico et al 1994, Yoon et al 1994), intraventricular haemorrhage (Yoon et al 1994, Gaziano et al 1994) and abnormal neurological assessment at 18 months (Valcamanico et al 1994). In addition fetuses with abnormal umbilical artery Doppler studies are more likely to be delivered preterm, to be delivered for fetal distress (Trudinger et al 1991) and not surprisingly have longer hospital stays than fetuses from high risk pregnancies with normal umbilical artery Doppler studies (Trudinger et al 1991, Gaziano et al 1994). It is not clear from these non-randomised studies whether the earlier gestation at delivery reflects action based on the knowledge of the abnormal Doppler findings or truly reflects the subgroup of fetuses with more serious problems which result in earlier delivery (Alfirevic & Neilson 1996). The best way to resolve this uncertainty is in the context of a randomised controlled trial.

These observational studies clearly demonstrated that fetuses with very abnormal Doppler waveforms were more likely to have poor outcomes. However from these studies it was not possible to determine whether the information provided by umbilical artery Doppler studies conferred any additional benefit, in pregnancies which usually had other indicators of high risk. If Doppler had been widely introduced into clinical practice based on the results of these observational studies it could have resulted in harm, e.g inappropriately early delivery of the preterm fetus with abnormal umbilical artery Doppler studies.

Fortunately the evolution of the role of umbilical artery Doppler studies in obstetric practice is unique in that it has been evaluated much more extensively in randomised controlled trials than other previous methods of fetal surveillance or investigation.

2.4.2 Randomised Studies

There are 20 randomised controlled trials reporting the use of umbilical artery Doppler ultrasound during pregnancy (Neilson & Alfirevic 1996). Eleven of these trials (n=6965 women) were performed in high risk pregnancies and are published as a meta-analysis in the Cochrane Library (Neilson & Alfirevic 1996). In six of these trials use of Doppler was compared with no use (in the control group) and in the remaining five trials Doppler studies were performed in the control group but were concealed from the women and the clinical staff.

The use of umbilical artery Doppler in high risk pregnancy (preeclampsia and/or suspected SGA) was associated with a 29% reduction in the odds of perinatal death (95% CI 0.50-1.00) (Neilson & Alfirevic 1996). Its use was also associated with fewer

hospital admissions during pregnancy OR 0.56 (95% CI 0.43-0.72), fewer labour inductions OR 0.83 (95% CI 0.74-0.93) and fewer caesarean sections for fetal distress OR 0.42 (95%, CI 0.24-0.71). In one study the outcome of delivery at <34 weeks was reported (n=476). The group which had Doppler studies performed had a significantly higher risk of delivery at <34 weeks OR 3.36 (95% CI 1.20-9.38). The coincident reduction in caesarean section for fetal distress and perinatal mortality suggests that knowledge of Doppler results assisted in determining the optimum timing of delivery. In this most recent meta-analysis performed in 1996, one large study (McParland & Pearce 1988) which had been included in the previous systematic review (Neilson & Alfirevic 1995) was excluded because of concerns about the veracity of the data. This resulted in wider confidence intervals for the reduction in perinatal mortality than had previously been reported, and some reduction in the confidence with which the reduction in perinatal mortality could be attributed to the use of Doppler ultrasound. Despite this a number of other additional benefits from the use of Doppler ultrasound were also demonstrated. Neilson & Alfirevic (1996) concluded that there is evidence to support the use of umbilical artery Doppler studies in high risk pregnancies. They also acknowledged that a case could be made for a larger trial than had previously been undertaken to confirm the effect on perinatal mortality. Most clinicians are now sufficiently convinced of the beneficial effects of umbilical artery Doppler studies to recommend its use in pregnancies with suspected SGA fetuses and preeclampsia (Maulik 1995, Alfirevic & Neilson 1996). As a result a large trial where umbilical artery Doppler is not performed or results are withheld, is unlikely to be performed in the future.

2.5 CEREBRAL DOPPLER STUDIES

When fetal sheep are made hypoxemic there is a marked increase in blood flow to the brain, heart and adrenals, and a decrease in supply to the carcass (Cohn et al 1974, Peters et al 1979). This redistribution of cardiac output is known as the 'brain sparing effect'. Using pulsed Doppler and more recently colour Doppler ultrasound, it is possible to obtain Doppler flow velocity waveform recordings from specific vessels within the fetal cerebral circulation. Data from these Doppler studies provide supportive evidence that the 'brain sparing effect' also occurs in humans. Several authors have found lower resistance indices in the cerebral circulation in SGA fetuses with abnormal umbilical artery Doppler studies (Wladimiroff et al 1986, Arduini et al 1992, McCowan & Duggan 1992). In a study of SGA fetuses undergoing cordocentesis, middle cerebral artery Doppler studies were performed prior to blood sampling (Vyas et al 1990). A significant quadratic relationship was found between fetal hypoxaemia and the degree of reduction in middle cerebral artery pulsatility index. The maximum reduction in pulsatility index occurred when fetal pO_2 was two to four SD below the mean for gestation. When the oxygen deficit was greater a rise in pulsatility index was found. The relationship between hypoxaemia and abnormal fetal cerebral Doppler studies is also supported by the fact that administration of oxygen to the mother can normalise these cerebral Doppler indices (Arduini et al 1988).

The reduction in fetal cerebral resistance indices, reflecting cerebral vasodilatation, is now thought to be a physiological adaptation rather than a pathological response. Serial studies have shown that these changes can occur in the SGA fetus up to six weeks before delivery is indicated for fetal reasons (Arduini et al 1992, McCowan &

Duggan 1992). Normalisation of cerebral Doppler indices has been found to occur preceding the onset of abnormalities in other tests of fetal wellbeing (Forouzan et al 1996) and also prior to fetal death (Mari et al 1991, Chandran et al 1991). It is hypothesised that the changes (increasing cerebral resistance indices) which occur with deteriorating fetal condition may reflect loss of cerebral autoregulation.

Alternatively they may occur secondary to impaired myocardial contractility (Arduini & Rizzo 1992).

Several authors have calculated ratios of cerebral/umbilical resistance indices in SGA fetuses and related the ratios to perinatal outcome (McCowan & Duggan 1992, Arduini & Rizzo 1992, Gramellini et al 1992, Arias 1994). Most have found that the ratio performs better than umbilical or cerebral Doppler resistance indices alone in predicting adverse pregnancy outcome. These studies have been performed for the most part in fetuses with severe growth restriction, who had abnormal umbilical artery Doppler studies. Previously there has been no published data addressing the utility of these ratios in predicting adverse outcome in SGA fetuses with normal umbilical artery Doppler studies. Data on cerebral/umbilical resistance ratios from a cohort of SGA fetuses with normal umbilical artery Doppler studies is presented in chapter 6.

2.6 UTERINE ARTERY DOPPLER STUDIES

So called idiopathic fetal growth restriction is often accompanied by reduced uteroplacental perfusion (Karr et al 1980, Nylund et al 1983) due to a failure of normal trophoblastic replacement of the spiral arteries (Khong et al 1986). Doppler resistance indices reflect impedance and therefore give an indirect assessment of blood flow. Using colour Doppler it is possible to obtain Doppler waveforms from the

uterine artery before it enters the myometrium (North et al 1994). High uterine artery Doppler resistance indices are common in pregnancies with preeclampsia and SGA (Trudinger et al 1985¹, Trudinger et al 1985², McCowan et al 1988). Placental bed biopsies from women with abnormal uterine artery Doppler waveforms have shown defective physiological changes in the spiral arteries (Voigt & Becker 1992, Lin et al 1995). Uterine artery Doppler studies may also have a role in determining whether a fetus is small because of maternal or fetal reasons (Trudinger et al 1985¹).

The relationship between uterine and umbilical artery Doppler studies has only been described in detail in four previous studies of SGA pregnancies (Trudinger et al 1985¹, Trudinger 1985², Gudmundsson et al 1988, Kay et al 1991). None of these studies used colour Doppler and all uterine artery Doppler waveforms were recorded from the arcuate vessels in the myometrium rather than the main uterine artery. Two studies used continuous wave Doppler (Trudinger et al 1985¹, Trudinger 1985²) and two used pulsed Doppler ultrasound (Gudmundsson et al 1988, Kay et al 1991). All studies reported good fetal outcomes in SGA pregnancies with normal umbilical and arcuate Doppler studies. Pregnancies with abnormal umbilical artery Doppler studies had higher perinatal morbidity but the arcuate Doppler study result did not appear to modify this risk.

If SGA fetuses with normal umbilical artery Doppler studies are constitutionally small but otherwise normal, it would be expected that they would usually have normal uterine artery Doppler studies. There is little published data to confirm or refute this. In the study by Trudinger et al (1985²) 19 of 53 SGA fetuses had normal umbilical

artery Doppler waveforms and five of the 19 (26%) had abnormal arcuate Doppler waveforms. Similar results were obtained by Gudmundsson et al (1988). Of 129 SGA pregnancies, 83 had normal umbilical artery Doppler studies, of whom 22 (26%) had abnormal arcuate Doppler studies.

The relationship between umbilical and uterine artery colour Doppler studies in SGA pregnancies is reported in chapters 6 and 7 of this thesis. The role of uterine artery Doppler studies in the prediction of perinatal morbidity is also discussed (chapter 6).

CHAPTER 3

INFLUENCE OF PERINATAL VARIABLES ON GROWTH AND NEURODEVELOPMENTAL OUTCOMES IN SGA INFANTS

3.1 INFLUENCE OF PERINATAL VARIABLES ON GROWTH

3.1.1 General

Few studies have addressed the influence of perinatal variables on long term growth. In 1997 Leger et al published the results of a study where the aim was to identify any parameters present at birth which might predict short stature at two years of age. A cohort of 317 SGA neonates (birthweight <3rd percentile) were measured at birth, 1, 3, 6, 12, 18 and 24 months. Length, weight and head circumference were measured as standard deviation scores (SDS). Children with congenital or chromosomal abnormalities (n=34) were not excluded. Over the course of the study 25% of children were lost to followup. In multiple linear regression analysis gestational age, birth length (SDS), target height (SDS) and maternal tobacco consumption were found to be the strongest predictors of height at two years. These parameters (present at birth) could explain 47% of the variability of height gain (SDS). Risk factors for short stature at two years were: reduced gestational age at delivery [OR 2.1 (95% CI 1.1-4.1)], the greater the deviation of birth length and target height [OR 1.9 (95% CI 1.4-2.7)]. Using a model incorporating gestational age, birth length (SDS) target height (SDS) and tobacco consumption, short stature could be predicted in 57 of 59 children (sensitivity 97%) who were short at two years of age, and normal stature was predicted in 142 of 159 children (specificity 89%).

3.1.2 Antenatal variables

Few investigators have addressed the effect of antenatal variables on subsequent postnatal growth (Fancourt et al 1976, Marsal et al 1998, Yoshimura et al 1998). The relationship between the gestation of diagnosis of IUGR in fetal life and postnatal growth has only been reported in one series (Fancourt et al 1976). Babies who were diagnosed with growth restriction at <34 weeks gestation were more likely to be small at four years.

Only two studies have specifically assessed the influence of antenatal Doppler variables on long term growth (Marsal et al 1998, Yoshimura et al 1998). In Marsal's study, aortic Doppler waveforms were measured prior to delivery in 151 children with IUGR at birth. Growth was subsequently assessed at seven years of age (Marsal et al 1998). Children with abnormal aortic Doppler waveforms were more growth restricted at birth and had increased initial catch up growth in weight and length. After adjustment for the more marked growth restriction at birth, abnormal aortic Doppler studies were not related to catch up growth in height or weight at seven years. Yoshimura et al (1998) assessed whether antenatal middle cerebral / umbilical artery pulsatility index ratios could be used to predict later growth. An abnormal ratio was found to predict complications in the newborn period but was not related to size at six or 12 months of age.

A number of studies have shown that most catchup growth in height and weight in SGA babies has occurred by six months of age (Fitzhardinge 1989, Leger et al 1997, Albertsson-Wikland 1997). In chapter 8 of this thesis postnatal growth at six months in a cohort of 203 SGA babies is reported. The influence of perinatal variables on

growth at six months, especially the time of diagnosis of SGA, newborn birth measurements and antenatal Doppler studies, is reported.

3.1.3 Severity Of Growth Restriction At Birth

Ponderal index [weight (g) x 100 ÷ length (cm)³] is a measure of the severity of growth restriction at birth, as babies with low length as well as weight will usually have normal ponderal indices. The relationship between ponderal index at birth and subsequent postnatal growth has been evaluated in two studies (Villar et al 1984, Tenovuo et al 1987). In the study by Villar et al (1984) term SGA babies with normal ponderal indices had smaller heads and were shorter at birth. Growth was assessed up to 30 months of age. Catch up growth occurred in those with low ponderal indices in the first few months after birth. Those with normal ponderal indices at birth remained lighter, shorter and had smaller head circumferences at 30 months than those with low ponderal indices. In a large study (n=488) long term growth was assessed in a group of term SGA infants in relation to ponderal indices at birth (Tenovuo et al 1987). Twenty six percent of children were still small at two years (weight <2.5th percentile) and infants with low ponderal indices at birth had better postnatal growth than those with normal ponderal indices.

Only three studies have reported the relationship between the severity of growth restriction at birth, as measured by standard deviation scores (SDS) below the mean, and subsequent postnatal growth (Hokken-Koelega et al 1995, Leger et al 1997, Marsal et al 1998). Hokken-Koelega et al (1995) reported that SGA babies with the largest birth length SDS below the mean were those least likely to catch up in height by two years. Leger et al (1997) also found an independent association between

birth length SDS and low height at two years. Marsal et al (1998), in a followup study of 151 children who were SGA at birth, found that the magnitude of the deficit in weight and length at birth was still predictive of weight and height at seven years.

3.2 INFLUENCE OF PERINATAL VARIABLES ON NEURODEVELOPMENTAL OUTCOME

3.2.1 Gestation At Diagnosis Of SGA

As outlined in chapter 1, SGA babies, both term and preterm, are more likely than AGA babies to experience adverse neurodevelopmental outcomes. A number of studies have addressed the influence of specific perinatal variables on subsequent neurodevelopment. The relationship between the gestation at which SGA was diagnosed antenatally, and later neurodevelopmental outcome, has only been reported in two papers based on the same cohort of SGA children (Fancourt et al 1976, Harvey et al 1982). At the time that this study was conducted SGA was diagnosed on the basis of a small fetal head (biparietal diameter) and abdominal circumference measurements were not yet performed. Children who had a small head size at <26 weeks gestation had a lower developmental quotient at four (Fancourt et al 1976) and five years of age (Harvey et al 1982) compared with children who had later slowing of head growth.

3.2.2 Severity Of Growth Restriction

There is conflicting evidence about the relationship between the severity of growth restriction and neurodevelopmental outcome. A recent study (Ley et al 1996²) found a relationship between the degree of birthweight deviation and global IQ of ≤ 85 when tested at six years of age in a group of children from high risk pregnancies 41% of

whom were SGA at birth. Similarly, minor neurological dysfunction at six years in the same children was also associated with the degree of birthweight deviation (Ley et al 1996₁). In contrast, another recent followup study (Soothill et al 1995) of children borne with severe IUGR, was not able to find an association between the degree of growth restriction (birthweight standard deviation scores) and neurodevelopmental testing at a mean age of 28 months.

In a further followup study of SGA babies (n=236) born between 1985 and 1990, the severity of growth restriction predicted neonatal morbidity but not abnormal Bayley test results at 12 or 24 months (Spinillo et al 1995).

3.2.3 Doppler Studies

a) Aortic and umbilical artery Doppler studies

There are five published studies which have evaluated neurodevelopmental outcome in high risk newborn infants (usually SGA) in relation to the degree of Doppler abnormality in the aorta (Ley et al 1996^{1,2}) or umbilical artery (Wilson et al 1992, Todd et al 1992, Valcamanico et al 1994). The two reports relating aortic Doppler waveform results to neurologic outcome at seven years of age are from the same cohort of 149 children (41% of whom were SGA at birth). Data was collected prospectively on fetal growth measurements, aortic Doppler waveforms, antenatal cardiotocography, gestational age at delivery and socioeconomic status. In addition, data was also collected about a range of obstetric risk factors and neonatal outcomes. In the first study the aim was to evaluate the role of aortic Doppler waveforms in predicting minor neurological dysfunction at seven years (Ley et al 1996¹). The two variables which best predicted the more severe type of minor

neurological dysfunction were abnormal aortic Doppler waveforms and male sex. Less severe minor neurological dysfunction was best predicted by increasing birthweight deviation and male sex.

In the second report (Ley et al 1996²) overall intellectual ability (verbal and global IQ) was assessed at 6.5 years. Both verbal and global IQ were less in children who had had abnormal aortic Doppler waveforms (global IQ 96 ± 15.7 in those with abnormal aortic Doppler studies versus 102 ± 13.2 in those with normal studies, $p < 0.05$). After assessing the effect of many perinatal variables in a logistic regression model, the best predictors of a global IQ ≤ 85 were found to be the combination of abnormal aortic Doppler waveforms, gestational age at delivery and social group. In this study neither the degree of growth restriction nor preterm delivery was associated with low IQ. However the children in this study were not born very preterm (earliest gestation at delivery 29 weeks, and the mean 35 weeks). The authors have speculated that the abnormal aortic Doppler waveforms reflect fetal hypoxia and that this might be the explanation for the poorer outcomes in those with abnormal studies.

Three small studies have addressed the value of umbilical artery Doppler waveforms in predicting neurodevelopmental outcome in children from high risk pregnancies. The first was a pilot study (Wilson et al 1992) where 40 children who had been referred to a high risk pregnancy clinic had a Denver Developmental Screening test performed, at a median postnatal age of 57 months. One third of these children were SGA at birth. No significant differences were found in terms of adverse neurological development between those with normal and abnormal umbilical artery Doppler waveforms however the study did not have sufficient power to detect a difference if

one existed. There were other problems with this study in that fetuses with abnormal umbilical artery Doppler studies were born on average four weeks earlier than those in the comparative normal Doppler group.

In the next study, addressing the role of umbilical artery Doppler in the prediction of adverse neurological outcome, the subjects were 31 SGA fetuses with absent or reversed end-diastolic velocity (Valcamanico et al 1994). This study is also similarly flawed as the control group (SGA and normal umbilical artery Doppler studies) were born four weeks later than those in the abnormal Doppler group. Overall 90% of children in the normal Doppler SGA group were neurologically normal at 18 months compared to 65% in the abnormal Doppler study group. These differences were not statistically significant however the authors erroneously conclude that 'these differences are extremely important from a clinical point of view.'

Todd et al (1992) investigated development at two years of age in children who were SGA at birth and were electively delivered at <34 weeks. Outcome was related to antenatal fetal heart rate patterns and also to umbilical artery Doppler findings. Only 54% (42/78) of eligible children were followed up. Thirty eight percent of these children had an abnormal antenatal fetal heart rate pattern (baseline variability < 5 beats per minute and no accelerations with or without late decelerations) and 40% had abnormal umbilical artery Doppler studies. Outcome was compared with a gestation matched group of AGA children with spontaneous preterm birth and a group of AGA children delivered at term. No differences in mental development index scores were detected on the basis of Doppler results in the electively delivered group. When compared with the control groups more children in the abnormal fetal

heart rate group failed at least one item (31%) on the Denver Developmental Screening Test compared with the preterm (5%) and term (3%) control groups ($p < 0.01$).

b) Cerebral Doppler studies

Two studies have reported the relationship between antenatal cerebral Doppler studies and neurologic outcome in the first year of life (Scherjon et al 1993, Chan et al 1996). In the earlier study of 117 high risk fetuses (delivered between 25 and 33 weeks) a ratio was calculated of the umbilical / cerebral pulsatility index obtained within a week of delivery. A ratio of >0.72 was defined as abnormal. No difference was found in neonatal ultrasound appearances nor in formal neurological examination at 12 months of age in those with abnormal compared to normal ratios.

In the second study of 74 high risk pregnancies, weekly Doppler studies were performed until delivery (Chan et al 1996). Neonatal morbidity and neurologic morbidity (at one and six months) were assessed in relation to middle cerebral artery Doppler findings before delivery. The ratio of umbilical to middle cerebral artery resistance index was a sensitive marker for SGA (sensitivity 78%). However infants with high ratios (>1) did not have a higher prevalence of perinatal complications or subsequent neurologic handicap. The result of this and the previous study would suggest that the cerebral vasodilatation (reflected by a low cerebral resistance index (RI) and high umbilical / cerebral RI ratio) is a physiological response to hypoxia and not a pathological finding.

c) *Summary*

There are few well designed studies that have evaluated long term neuro-developmental outcome in relation to antenatal Doppler variables. The data to date would suggest that low resistance in the cerebral circulation is not associated with adverse long term neurodevelopmental outcome. Further studies are necessary to confirm whether abnormal Doppler findings in the umbilical artery and aorta are independent predictors of long term adverse neurodevelopmental outcome or whether abnormal Doppler is a marker of more severe growth restriction and / or a more preterm fetus. The relationship between perinatal variables, including antenatal Doppler studies, and neurodevelopmental outcome in SGA children at 18 months is the subject of the study reported in chapter 9 of this thesis.

3.2.4 Acidosis

SGA fetuses who are chronically acidotic before birth may also be at increased risk of impaired neurodevelopment (Soothill et al 1992, Soothill et al 1995). In the first study, 36 children with normal karyotype, who were born after 32 weeks, and had prenatal cordocentesis for severe IUGR, had neurodevelopment assessment performed at a mean age of 29 months (Soothill et al 1992). Neurodevelopment was compared between 13 (36%) acidemic fetuses (pH <2SD below mean for gestation) and 23 (64%) non acidemic fetuses. Acidemic fetuses had a lower Griffiths developmental score (mean 98, SD 6.3) than non acidemic (mean 100.3 SD10.3 p=0.01). A significant correlation between the degree of acidemia and the developmental quotient was found but not between the degree of growth retardation and the developmental quotient. The results of this study need to be interpreted with some caution as there were at least three possible confounders which may have

effected the results. The acidemic fetuses were delivered earlier (34.5 versus 36 weeks) weighed less (1559 g versus 1824 g) and their mothers were more likely to smoke. The same group (Soothill et al 1995) have also reported on neuro-developmental outcome in a larger series of SGA children (n=65) in relation to pH at cordocentesis. They do not state whether this series includes the group reported in their previous publication (Soothill et al 1992). In this latter study fetal pH was inversely correlated with developmental quotient at a mean age of 28 months. No association was found between developmental quotient and gestational age at delivery or severity of growth restriction.

3.2.5 Ponderal Index

Villar et al (1984) assessed neurodevelopment in a group of 49 term SGA infants at three years of age in relation to ponderal index at birth. Outcome was also compared with a group of AGA term controls. The SGA children with normal ponderal indices at birth were lighter, shorter, and had smaller head circumferences at three years. These children scored lowest in seven out of eight developmental assessments and had the lowest composite developmental scores. Those with a low ponderal index at birth had intermediate values on neurodevelopmental testing, scoring between the AGA and normal ponderal index groups.

In another study (Berg et al 1989) where SGA children were grouped according to ponderal indices, hypoxia in the perinatal period, but not ponderal index, was predictive of neurological morbidity at seven years.

In our study of the relationship between neurodevelopmental outcome at 18 months and perinatal variables, data is also presented on ponderal index and cord arterial pH (chapter 9).

CHAPTER 4

GENERAL METHODS

4.1 ANTENATAL STUDIES

4.1.1 Study Participants And Plan Of Research

The antenatal studies reported in this thesis were carried out between March 1993 and July 1997 and were approved by the regional ethics committee. Women with singleton pregnancies between 24 and 36 completed weeks of gestation, who were suspected on the basis of ultrasound, to have a SGA fetus, were invited to participate. The other requirements for inclusion were an ultrasound scan at ≤ 20 weeks and no ultrasound evidence to suggest fetal abnormality. Women who met these criteria were referred to the research midwife from hospital departments (ultrasound, antenatal clinic, assessment unit, and the antenatal ward) as well as from private doctors and midwives. An umbilical artery Doppler study was performed at this time.

The research midwife provided detailed explanation about the study, as well as a written information leaflet. The women were then given a couple of days to consider the information prior to making a final decision about participating in the study and signing the consent form. After consenting a repeat umbilical artery Doppler study was performed. If this study and the preceding study (two or three days earlier) were both abnormal, the women entered the abnormal Doppler study. If both umbilical artery Doppler studies were normal they entered the normal Doppler study (fig 4.1). If one study was normal and one was abnormal a further umbilical artery Doppler study was performed which determined the study group allocation.

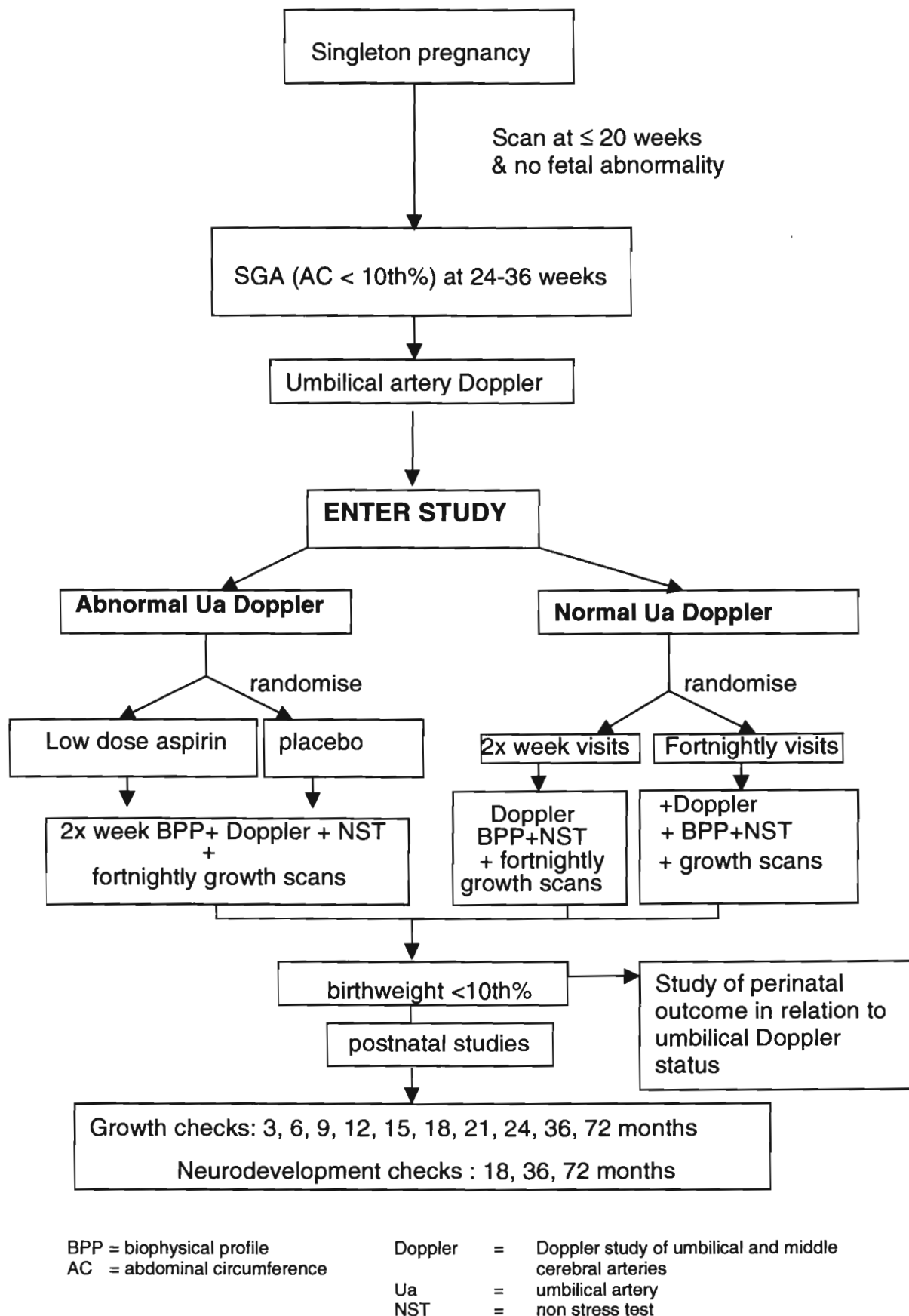


Fig 4.1 Plan Of Research : Flow Chart

If the estimated date of delivery calculated from menstrual dates differed from that calculated by scan by more than 10 days the scan estimated ate of delivery was used (Gardosi et al 1997).

a) Abnormal Doppler, low dose aspirin study

When the resistance index (RI) in the umbilical artery was >95th% according to our previously established normal range (Duggan & McCowan 1993) women were randomly allocated to treatment with aspirin 100 mg or identical placebo (fig 4.1).

The hypothesis was that low dose aspirin treatment would increase birthweight. This trial is presented in chapter 5.

b) Normal Doppler, fetal surveillance study

When the umbilical artery Doppler resistance index was within the normal range (≤ 95 th %) women entered a pilot randomised controlled trial where they were randomly allocated to receive either planned fortnightly or planned twice weekly fetal surveillance (see fig 4.1). The hypothesis was that the reduced frequency of fetal surveillance would not increase maternal or fetal morbidity and this trial is presented in chapter 6.

c) Perinatal outcome in relation to umbilical artery Doppler status

In this study perinatal outcome was compared, according to umbilical artery Doppler status, in the participants in the two randomised trials who gave birth to SGA babies (fig 4.1).

4.1.2 Ultrasound Equipment

Ultrasound and Doppler measurements were obtained using one of two colour Doppler machines;

- i) Toshiba 270 (Toshiba Medical Systems, Tokyo, Japan) using a 3.75 MHz convex array or a 3.5 MHz phased array sector transducer. The maximum power output of this machine is 89 mW/cm², spatial peak temporal average.

- ii) A Diasonics masters series (Diasonics, California, USA) with either a 3.5 MHz convex array or a 5 MHz phased array sector transducer. The maximum power output for the 3.5 MHz and 5MHz probes are 91 mW/cm² and 93.9 mW/cm² respectively, spatial peak temporal average.

4.1.3 Ultrasound Measurements

All scans were performed in a semi-recumbent position by trained sonographers in the Ultrasound Department at National Women's Hospital, under the supervision of obstetricians or radiologists. A fetus was classified as small for gestational age if its abdominal circumference on ultrasound scan was <10th% for gestation (Campbell 1976). Repeat growth scans were performed at fortnightly intervals until delivery. Measurements were also obtained of the biparietal diameter, head circumference and femur length using standard techniques.

4.1.4 Doppler Studies

Doppler studies were performed with the women in a semirecumbent position. Waveforms were recorded during fetal apnea and inactivity. In all cases the high

pass filter was set at 100 mHz or less so that frequencies generated by red cells with low velocities were not lost.

a) Umbilical artery

Umbilical artery Doppler studies were obtained from a mid segment of umbilical cord. This site was chosen as recordings taken from the placental end result in lower resistance indices compared to recordings obtained at the abdominal end, in both normal and growth restricted pregnancies (Skoll et al 1997). The angle of insonation was adjusted to obtain the tallest possible Doppler waveforms and attempts were made to also obtain a concurrent image of umbilical venous flow to check that the fetus had not started breathing. When good quality waveforms were obtained the image was frozen and a RI (Pourcelot 1982) was calculated from a mean of five waveforms (fig 2.2), as this results in more reproducible ratios than when calculated from fewer waveforms (Erskine et al 1985). The RI was selected as the preferred mathematical ratio to describe the Doppler maximum frequency envelope for two reasons. Firstly, previous studies in our hospital have shown that the RI was reproducible between the two types of ultrasound machines used for this study whereas the pulsatility index was not (Duggan & McCowan 1993). Secondly the RI has been found to perform better than the systolic-diastolic ratio or the pulsatility index in predicting adverse perinatal outcome (Maulik et al 1991).

b) Middle cerebral artery

An axial view of the fetal head was obtained at the level of the cerebral peduncles. Using colour Doppler, the middle cerebral artery was identified in the lateral sulcus after its origin from the internal carotid artery (Van den Wijngaard et al 1989). The

sample volume was set at 2 to 3 mm and the angle of the beam adjusted to $<60^\circ$ in order to obtain a tall Doppler waveform. The RI was calculated from a mean of five waveforms. If it was not possible to obtain a good recording within one to two minutes the examination was abandoned. In the abnormal Doppler study umbilical and cerebral Doppler studies were performed twice weekly and in the normal Doppler study they were performed either fortnightly or twice weekly (fig 4.1). When both middle cerebral and umbilical artery Doppler studies were performed within two weeks of delivery a ratio of middle cerebral RI/umbilical RI was calculated. This ratio was defined as abnormal if the result was <1 (Arias 1994).

c) Uterine artery

Doppler studies were obtained from the left and right uterine arteries using colour Doppler ultrasound at fortnightly intervals in both normal and abnormal Doppler study groups. The sample volume was positioned at the apparent crossing of the uterine and external iliac arteries and a RI was calculated from a mean of five waveforms (North et al 1994). An abnormal uterine artery Doppler study was defined as a RI in at least one uterine artery of >0.58 (Jacobson et al 1990).

4.1.5 Fetal Assessment

a) Antenatal fetal heart rate monitoring

Fetal heart rate monitoring was performed by the research midwife at least twice weekly in pregnant women in the abnormal umbilical artery Doppler study and at planned twice weekly or fortnightly intervals in those in the normal Doppler study (fig 4.1). Fetal heart traces were classified as reactive (≥ 2 accelerations of at least 15 beats per minutes lasting ≥ 15 seconds during the monitoring period (up to 60

minutes) or non reactive (<2 accelerations and/or accelerations of <15 beats per minute and/or accelerations lasting <15 seconds) (ACOG 1994).

b) Biophysical profile score

Biophysical profile scores were measured at least twice weekly from fetuses in the abnormal Doppler study and at either planned fortnightly or twice weekly intervals in those in the normal Doppler study (fig 4.1). A modified Manning score was calculated with a maximum score of 8/8 (Manning et al 1979) comprised of assessments of breathing, movement, tone, and liquor volume.

4.1.6 Clinical Management

Fetal monitoring, ultrasound and Doppler scans were coordinated by the research midwife and results were communicated to the referring clinician who was responsible for management decisions.

4.1.7 General Definitions

- *Gestational hypertension* was defined as a blood pressure of at least 140/90 mmHg, with an increase of at least 15 mmHg in diastolic blood pressure, taken on two occasions more than four hours apart after the 20th week of pregnancy.
- *Pre-eclampsia* was defined as gestational hypertension and proteinuria of >300 mg/24 hours and/or at least '++' proteinuria on repeated testing with urine dipsticks, in the absence of urinary tract infection.
- *Pregnancy induced hypertension* referred to cases of gestational hypertension or preeclampsia.
- *SGA* was defined as birthweight <10th percentile (Guaran et al 1994).

- *Acidosis* at birth was empirically defined as cord arterial pH <7.15 and base excess <7.
- *Birth asphyxia* was empirically defined as acidosis at birth and/or a five minute apgar score <6.
- *Hypoglycemia* was defined as blood glucose <2.5 mmol/l >4 hours after delivery or requiring IV glucose therapy for hypoglycemia. Blood glucose monitoring was carried out in all babies of birthweight <2500g.
- *Ponderal index* = weight (g) x 100 ÷ (length cm)³

4.1.8 Newborn Measurements

Birthweight was the first recorded weight after birth (usually within the first few minutes) measured using electronic scales accurate to within 5g. Placental weight (not trimmed) was also measured by the birth attendant using the same electronic scales.

Other measurements were obtained by the research midwife within 48 hours of birth.

Birth length (cm) was measured to the nearest mm in an infant measuring box (neonatometer). Head circumference (maximum occipito-parietal circumference) was measured with a disposable tape measure to the nearest mm.

4.2 POSTNATAL STUDIES

Participants in the antenatal studies who delivered SGA babies (birthweight <10th percentile (Guaran et al 1994) were asked to enter their babies in the postnatal studies of growth and neurodevelopmental outcome (figure 4.1). Growth assessments were performed at three monthly intervals until 24 months, beginning at

three months corrected age. Neurodevelopmental assessments were performed at 18, 36 and 72 months corrected age at which time growth was also measured.

To increase the sample size of the postnatal studies, SGA babies who had not taken part in the antenatal studies were also invited to participate if: a scan had been performed at ≤ 20 weeks gestation, they had been recognised as SGA in pregnancy, an umbilical artery Doppler study had been performed within two weeks of delivery and there was no evidence of chromosomal or congenital abnormality detected in the newborn period. Specific methods for the postnatal studies are described in chapters 8 and 9.

4.3 DATA

The author checked and where necessary corrected the data used in the analyses for the studies reported in this thesis.

4.4 STATISTICAL ANALYSES

Sample size calculations are discussed in each chapter. Unless otherwise stated sample size calculations are for power of 80% and $\alpha=0.05$.

In all studies, when data were normally distributed, differences between continuous variables were compared using the unpaired student t-test. When data were not normally distributed, differences between continuous variables were compared using the Mann Whitney U test. Chi-square or Fishers exact test (for cell counts <5) were used for comparisons between groups. Additional statistical methods are described in each chapter.

A large part of the statistical analysis for chapter 4 of this thesis was performed (using the SAS system 6.12 statistical package) by Mr A Stewart, Health Research Council Statistics Unit, Department of Community Health, Auckland School of Medicine. The analyses for the remaining chapters using Statview (SAS Institute 2nd edition 1998) were carried out by the author with advice from Mr A Stewart when necessary.

CHAPTER 5

A RANDOMISED CONTROLLED TRIAL OF LOW DOSE ASPIRIN TO INCREASE BIRTHWEIGHT IN SMALL FOR GESTATIONAL AGE PREGNANCIES WITH ABNORMAL UMBILICAL ARTERY DOPPLER STUDIES

5.1 INTRODUCTION

Intrauterine growth restriction is an important clinical problem resulting in morbidity and mortality in fetal life and the newborn period (Seeds & Peng 1998). Neurodevelopmental problems are more common in childhood (Wallace & McCarton 1997) and recent data strongly supports a link between poor fetal growth and adult cardiovascular diseases (Barker 1997). If there was an effective treatment which could augment growth of the undernourished fetus prior to birth perhaps some of these later complications could be reduced.

Prostacyclin is a potent vasodilator and inhibitor of platelet function. In pregnancies complicated by IUGR, placental (Jogee et al 1983) and umbilical arterial prostacyclin production have been reported to be reduced (Dadak et al 1982). The ratio between prostacyclin and thromboxane is thought to be important in the regulation of platelet and vascular function. Low dose aspirin (100 mg) has minimal effect on prostacyclin production but is a potent inhibitor of thromboxane (Ylikorkala et al 1986). It therefore alters the ratio of prostanoids in favour of improved perfusion and could enhance fetal growth.

A number of studies have therefore assessed the role of low dose aspirin treatment for the prevention of IUGR (Uzan et al 1990, CLASP 1994, Italian Study of Aspirin in Pregnancy 1993) and the results have been mixed. A recent meta analysis of 13 studies (Leitch et al 1997) showed a significant reduction in growth restriction with aspirin prophylaxis (OR 0.87, 95% CI 0.76-0.99) especially when treatment was initiated before 17 weeks gestation (OR 0.35, 95% CI 0.21-0.58) and with doses of 100 or 150 mg daily (OR 0.36, 95% CI 0.22-0.59).

The role of aspirin as a therapy for IUGR has only been reported in three randomised placebo controlled trials (Trudinger et al 1988, CLASP 1994, Newnham et al 1995). In the first study (Trudinger et al 1988) 46 women whose fetuses had abnormal umbilical artery Doppler studies (35/46 with suspected IUGR) were randomised to treatment with 150 mg aspirin or placebo. Intention to treat analysis was not reported. After subgroup analysis, fetuses with abnormal umbilical artery Doppler waveforms (n=34) treated with aspirin (n=14) had a 526 gm increase in birthweight and an increase in head circumference and placental weight compared with placebo treated (n=20). Aspirin treatment did not increase birthweight in those with absent end-diastolic velocity (n=12).

In a more recent study by Newnham et al (1995), 51 pregnant women with fetuses with IUGR and abnormal umbilical artery Doppler waveforms were randomised to treatment with aspirin 100 mg or placebo. This trial was terminated early, prior to recruitment of the full sample size, following the negative findings in the CLASP trial (1994). No benefit of aspirin treatment was demonstrated in Newnham's study.

In CLASP, the largest study of aspirin treatment of IUGR, 261 women with suspected IUGR (not necessarily confirmed by ultrasound) were randomly allocated to treatment with aspirin 60 mg or placebo. Umbilical artery Doppler studies were not part of the protocol for this study. Less than one third of study babies were growth restricted at birth and no significant benefit of aspirin treatment was found. This small dose of aspirin (60 mg) causes marked inhibition of maternal thromboxane (Benigni et al 1989) but inconsistent suppression of fetal thromboxane (Ritter et al 1987, Benigni et al 1989). Suppression of fetal thromboxane may theoretically be of benefit as infusion of the thromboxane analogue U46619 in the fetal lamb increased placental resistance and elevated systolic - diastolic ratios in umbilical artery Doppler waveforms (Trudinger et al 1989).

The question of whether aspirin is of benefit in the treatment of fetal growth restriction with a placental vascular lesion, indicated by abnormal umbilical artery Doppler waveforms, is therefore still unresolved.

The hypothesis of the current study was that antenatal treatment with 100 mg aspirin daily (for ≥ 14 days), given to mothers with small for gestational age fetuses and abnormal umbilical artery Doppler studies, would increase birthweight.

5.2 METHODS

5.2.1 General

Pregnant women with singleton pregnancies were eligible for recruitment to the study if they met the following criteria: ultrasound evidence suggesting a small for

gestational age fetus (abdominal circumference < 10th percentile, Campbell 1976), a previous anatomy scan at ≤ 20 weeks to confirm dates and with no evidence of fetal abnormality; a gestational age between 24 and 36 weeks; an umbilical artery Doppler resistance index >95th percentile for gestation (Duggan & McCowan 1993); no previous aspirin use during the pregnancy; no contraindications to aspirin use; and provided informed consent to participate in the study. Two umbilical artery Doppler results >95th percentile performed 2-3 days apart were necessary before recruitment.

Randomisation was by a telephone call to a person not involved in the study, who used computer generated numbers to assign women to aspirin or identical placebo. Patients and staff were blinded to treatment allocation. A dose of 100 mg of aspirin was used as this dose inhibits both maternal and fetal thromboxane production without affecting prostacyclin (Ylikorkala et al 1986). This higher dose of aspirin would, in theory, be more likely to improve placental blood flow than a lower dose. It was decided arbitrarily prior to commencement of the study that 14 days of aspirin treatment might be necessary to achieve a therapeutic effect and that women treated for ≥ 14 days would comprise the study group.

The methodology for the Doppler studies is described in chapter 4. After recruitment, Doppler studies, biophysical profile scores and nonstress tests were performed at least twice weekly and growth scans were performed at fortnightly intervals. The research midwife met the women at each hospital attendance, performed the non stress tests, checked that they were taking their tablets, and arranged the scans. She instructed all women to monitor fetal movements and to keep a kick chart.

A hospital guideline for the management of small for gestational age pregnancies recommended that delivery should not be undertaken on the basis of abnormal Doppler in the absence of other concerns regarding fetal wellbeing. Clinical management was continued by the referring clinician and additional tests could be ordered as clinically indicated.

Compliance was assessed by measuring thromboxane B2 by immunoassay (Patrono et al 1980) in maternal serum two weeks after recruitment to the study. Ten mls of venous blood was drawn and allowed to clot at 37°C for one hour and then centrifuged at 2000 rpm for 10 minutes before storage at -20°C.

Newborn measurements were carried out as described in chapter 4. Australian percentile charts (Guaran et al 1994) were used to categorise the birth measurements as there are currently no suitable New Zealand charts.

5.2.2 Statistical Methods

a) Sample size

At the time of commencement of the study (1993) the only previous similar published study (Trudinger et al 1988) had found a 526 g increase in birthweight with aspirin treatment. The sample size was therefore calculated to detect a 500 g difference in birthweight between treatment groups with a standard deviation of 700 g. Thirty one subjects were required in each arm, $\alpha=0.05$ and power = 80%.

b) Statistical analysis

Statistical analysis was performed using the SAS release 6.12 statistical package. Multiple regression analysis was used to determine whether the independent variables maternal height, weight, parity, age, ethnic group and smoking status had any effect on the dependent variables: newborn, weight, length and head circumference. Values are expressed as mean (SD) for normally distributed data, or median (range) for data which are not normally distributed. Other statistical methods are described in chapter 4.

5.3 RESULTS

Ninety nine women were recruited to the study at a mean gestation of 32 weeks. Sixty five were treated for ≥ 14 days and comprise the study group. Thirty two of these were treated with aspirin and 33 with placebo. Mean duration (standard deviation) of treatment did not differ between aspirin [30 (17) days] and placebo treated [29 (15) days $p=0.80$]. There were no differences between groups in maternal age, size, ethnicity, parity or smoking status (table 5.1).

Table 5.1: Characteristics of the women treated for ≥ 14 days

	Aspirin n=32	Placebo n=33	P value
Age (years)	27.6 (5.7)	29.0 (4.4)	0.27
Height (cm)	163 (6.4)	163 (6.1)	0.90
Weight at delivery (kg)	71.0 (15.1)	71.7 (15.2)	0.85
Ethnicity			
European	26 (81%)	19 (58%)	0.07*
Maori	3 (10%)	6 (18%)	
Pacific Island	0	2 (6%)	
Asian	2 (6%)	5 (15%)	
Other	1 (3%)	1 (3%)	
Parity			
0	12 (37%)	13 (39%)	0.34
1	13 (41%)	17 (52%)	
>1	7 (22%)	3 (9%)	
Smoking status			
(cigarettes per day)			
0	21 (68%)	19 (58%)	0.63
<20	8 (26%)	10 (30%)	
≥ 21	2 (6%)	4 (12%)	
Gestational age at recruitment (weeks)	31.6 (2.4)	32.1 (2.7)	0.44
RI at recruitment	0.79 (0.68-1.0)	0.78 (0.68-1.0)	0.39

RI= resistance index; Values are mean (SD), median (range), number (%) as appropriate; *For the comparison of European versus other racial groups

No significant differences in gestational age at delivery or any newborn measurements were found between aspirin and placebo treated women either in the whole group (table 5.2.a) or the group treated for ≥ 14 days (table 5.2.b).

Table 5.2.a Newborn data - whole study group

	Aspirin	Placebo	P value
	n=49	n=50	
Gestational age at delivery (wks)	34.4 (3.4)	34.9 (3.3)	0.50
Female sex	30 (61%)	29 (58%)	0.74
Birthweight (g)	1705 (715)	1787 (678)	0.56
Birthweight <10th%	37 (76%)	39 (78%)	0.77
Length (cm)	41.2 (5.9)	42.3 (5.2)	0.38
Length <10th%	37/48 (76%)	34/48 (71%)	0.48
HC (cm)	29.6 (3.8)	29.9 (3.2)	0.72
HC <10th%	20/48 (42%)	18/49 (37%)	0.62
Ponderal index	2.26 (0.30)	2.27 (0.33)	0.89
Ponderal index <10th%	15/48 (31%)	16/48 (33%)	0.83
Placental weight (g)	362 (124)	330 (116)	0.19

HC= head circumference

Values are mean (SD) or number (%) as appropriate

Table 5.2.b Newborn data - received treatment \geq 14 days

	Aspirin	Placebo	P value
	n=32	n=33	
Gestational age at delivery (wks)	35.9 (2.2)	36.2 (2.3)	0.59
Female sex	22 (69%)	18 (55%)	0.23
Birthweight (g)	1948 (616)	2029 (600)	0.59
Birthweight <10th%	25 (78%)	26 (79%)	0.95
Length (cm)	43.1 (4.3)	43.7 (4.6)	0.59
Length <10th%	24/31 (77%)	23/32 (72%)	0.61
HC(cm)	31.2 (2.4)	30.9 (2.7)	0.64
HC <10th%	10/31 (32%)	12/32 (38%)	0.66
Ponderal index	2.36 (0.28)	2.33 (0.33)	0.50
Ponderal index <10th%	10/31 (32%)	11/32 (34%)	0.86
Placental weight (g)	389 (115)	369 (116)	0.50

HC= head circumference

Values are mean (SD) or number (%) as appropriate

The relationship between newborn measurements and treatment groups remained the same after adjusting for maternal age, ethnicity, parity, height, weight and smoking in those treated for \geq 14 days. The same statistical analyses were also performed for those who were treated for \geq 21 days (n=40) and also after exclusion of the three who had absent end-diastolic velocity at recruitment and the two who were found after birth to have a congenital abnormality (data not shown). The results did not change.

Delivery method and measures of newborn morbidity were also not different between treatment groups (tables 5.3.a and 5.3.b).

Table 5.3.a Pregnancy outcome and newborn morbidity - whole study group

	Aspirin	Placebo	P value
	n=49	n=50	
Caesarean section	28 (57%)	22 (44%)	0.19
Caesarean section before labour	23 (47%)	19 (38%)	0.37
Preeclampsia	12 (24%)	9 (16%)	0.43
Gestational hypertension	10 (20%)	16 (32%)	0.19
Admitted to neonatal nursery	35 (71%)	37 (74%)	0.65
Time in neonatal nursery (days)	18 (0-125)	7 (0-50)	0.44
Perinatal death	4 (8%)	3 (6%)	0.67
Periventricular haemorrhage	0	2 (4%)	0.32
Birth asphyxia	5 (10%)	1 (2%)	0.11

Values are median (range) or number (%) as appropriate

Table 5.3.b Pregnancy outcome and newborn morbidity - received treatment ≥ 14 days

	Aspirin	Placebo	P value
	n=32	n=33	
Caesarean section	15 (47%)	11 (33%)	0.31
Caesarean section before labour	11 (34%)	8 (24%)	0.37
Preeclampsia	7 (22%)	4 (12%)	0.29
Gestational hypertension	9 (28%)	11 (33%)	0.65
Admitted to neonatal nursery	22 (69%)	22 (67%)	0.86
Time in neonatal nursery (days)	19 (0-125)	10 (0-45)	0.25
Perinatal death	0	3 (9%)	0.23
Periventricular haemorrhage	0	2 (6%)	0.49
Birth asphyxia	3 (9%)	1 (3%)	0.36

Values are median (range) or number (%) as appropriate

In the group treated for ≥ 14 days all caesarean sections in labour were performed for suspected fetal distress. Of the 11 caesarean sections performed before labour in the aspirin arm four were for IUGR, three for preeclampsia, three for suspected fetal distress and one for a breech. Of the eight prelabour caesarean sections in the placebo arm, five were for IUGR, one for preeclampsia, one for suspected fetal distress and one for antepartum haemorrhage.

In the whole study group there were seven perinatal deaths, four in aspirin treated and three in placebo treated. Five of these babies had a weight considered pre-viable in our institution at the time (<600 g) although active treatment was initiated for the three liveborn babies. One baby (birthweight 1405 g) died of congenital heart disease in the newborn period and one normotensive aspirin treated woman had a stillborn baby (birthweight 2380 g) as a result of a placental abruption at 36 weeks gestation. One other placebo treated woman had a placental abruption during the study which resulted in caesarean delivery of a live baby.

After birth two babies, one in each treatment group, were found to have congenital abnormalities (one congenital heart disease and one with multiple abnormalities). These two babies had long stays in the neonatal nurseries (125 days aspirin group and 22 days placebo group respectively). Length of stay in the neonatal nursery was therefore also calculated after exclusion of these two babies from the study group and no differences were found between aspirin and placebo groups (median length of stay in newborn nursery was 15 days for aspirin and 10 days for placebo $p=0.27$).

Median umbilical artery resistance indices fell as pregnancy continued and there was no difference in mean RI values at study entry (table 5.1) or at delivery 0.70 (0.60-1.0) in aspirin and 0.71 (0.52-1.0) placebo study groups.

Thromboxane B2 levels were measured in serum two weeks after randomisation to assess compliance with treatment. Samples were available for analysis in 53 of the 65 subjects. The median thromboxane B2 concentration in aspirin treated was 1

(range 0-6) pg/ml and in placebo treated was 97 (range 9-311) pg/ml. There was no overlap in thromboxane levels between the two groups.

5.4 DISCUSSION

In this study treatment with low dose aspirin 100 mg for ≥ 14 days (mean 30 days) did not increase birthweight or other measures of fetal growth in SGA pregnancies with abnormal umbilical artery Doppler studies. This lack of a therapeutic effect did not appear to be due to poor compliance with therapy, as the aspirin treated women had very low levels of thromboxane B2 in their serum at least two weeks after recruitment. The results of this study are in agreement with the similar but smaller study by Newnham et al 1995, and are also in keeping with the results of the CLASP study (1994).

This contrasts with the earlier study by Trudinger et al (1988) where treatment with aspirin 150 mg in pregnancies with fetuses with abnormal umbilical artery Doppler studies resulted in a 526 g increase in birthweight. The gestational age at entry and duration of treatment was almost identical to that in our study. The difference in results is unlikely to be explained by the difference in aspirin dosage as almost complete suppression of thromboxane B2 production occurred in our study with treatment with 100 mg aspirin. All cases in Trudinger's study had abnormal Doppler waveforms at recruitment but only 75% were thought to have established growth restriction at this time. The beneficial effect on growth reported in Trudinger's study might be explained by failure to do an intention to treat analysis or chance due to the small numbers in the subgroup analysis. Alternatively, the initiation of aspirin at an

earlier phase in the disease process in the former study, may explain the differences in results.

The rationale for trials of low dose aspirin treatment for prophylaxis or therapy of IUGR has been that the ratio of prostacyclin to thromboxane was thought to be shifted resulting in a dominance of thromboxane in IUGR pregnancies (Ylikorkala et al 1985). It had been reported in studies conducted in the 1980s that prostacyclin production was reduced in pregnancies with IUGR (Jogee et al 1983, Dadak et al 1982) and one study found suggestive evidence of increased thromboxane production in pregnancies with chronic placental insufficiency (Wallenburg et al 1982). However data from a recent study has shown that thromboxane production was not increased and the ratio of prostanoid production was not disturbed in either term or preterm placentae from IUGR pregnancies when compared with controls (Sorem & Siler-Khodr 1995). The current evidence is therefore conflicting as to whether disturbed prostanoid metabolism occurs in pregnancies with IUGR. If prostanoid metabolism is not consistently abnormal then low dose aspirin would not be expected to have a major therapeutic effect. The other possible explanation for the negative results in this and other studies (CLASP 1994, Newnham et al 1995) is that aspirin may not be effective once placental vascular pathology and growth restriction is well established.

5.5 SUMMARY

- * Treatment with low dose aspirin can not be recommended as a therapy antenatally for SGA pregnancies with abnormal umbilical artery Doppler studies.

too premature

CHAPTER 6

A PILOT RANDOMISED CONTROLLED TRIAL OF TWO REGIMENS OF FETAL SURVEILLANCE IN SMALL FOR GESTATIONAL AGE PREGNANCIES WITH NORMAL UMBILICAL ARTERY DOPPLER STUDIES

6.1 INTRODUCTION

Small for gestational age fetuses are a heterogeneous group comprising those with placental insufficiency, who are at high risk of perinatal complications; those who are small for genetic or racial reasons and are usually healthy at birth; and a small group with intrinsic fetal problems such as chromosomal or congenital abnormalities.

Umbilical artery Doppler studies appear to be able to assist in the classification of SGA fetuses into groups with varying degrees of fetal and newborn risks (Reuwer et al 1987, Burke et al 1990, Trudinger et al 1991, Snijders et al 1997). Those with abnormal umbilical artery Doppler studies have been found to have placental vascular pathology (Giles et al 1985, McCowan et al 1987, Krebs et al 1996) and are at increased risk of stillbirth, early delivery and newborn complications (Burke et al 1990, Trudinger et al 1991, Soothill et al 1993, Gaziano et al 1994) including periventricular haemorrhage (Gaziano et al 1994). In contrast, SGA fetuses with normal umbilical artery Doppler studies are less likely to be stillborn (Burke et al 1990) to require delivery for fetal distress (Dempster et al 1988, Burke et al 1990, Bekedam et al 1990) or to suffer morbidity in the newborn period (Burke et al 1990, Trudinger et al 1991, Gaziano et al 1994).

Because of the increased risk, when poor fetal growth is recognised before birth, some centres recommend hospitalisation so that fetal wellbeing can be carefully monitored (Nienhuis et al 1994). Others recommend frequent outpatient assessment unless there is particular concern about fetal or maternal wellbeing (Haley et al 1997). Recent publications which highlight the low morbidity in SGA fetuses with normal umbilical artery Doppler studies, have also suggested that more conservative management with less intervention could probably be safely implemented in these pregnancies (Burke et al 1990, Gaziano et al 1994). It has been recommended that prospective trials are conducted to 'substantiate these expectations' (Reuwer et al 1987).

Only one randomised trial has addressed the issue of less intervention in pregnancies with growth restriction and normal umbilical artery Doppler studies (Nienhuis et al 1997). This trial was performed in a centre where hospitalisation was usual practice for pregnancies with growth restriction. One hundred and fifty women were randomised either to an intervention group, where it was recommended that hospitalisation should not occur if umbilical artery Doppler studies were normal, or a control group, where usual care was provided but the Doppler results were concealed. No differences were found in the rates of hospitalisation or in newborn morbidity between study groups.

In our hospital outpatient management of SGA fetuses is usual and fetal surveillance has been recommended twice weekly. The current study was designed to test the hypothesis that the frequency of fetal surveillance could be safely reduced from twice

weekly to fortnightly in SGA pregnancies with normal umbilical artery Doppler studies without increasing morbidity for the baby or mother.

Secondary objectives were:

- 1) to assess the prevalence of abnormal cerebral/umbilical artery resistance index ratios and abnormal uterine artery Doppler studies
- 2) to determine whether abnormal studies could identify the subgroup of SGA pregnancies with normal umbilical artery Doppler studies which developed fetal or newborn morbidity.

6.2 METHODS

6.2.1 General

Pregnant women with singleton pregnancies, who were outpatients, were eligible for recruitment to the study if they met all of the following criteria: ultrasound evidence of SGA (abdominal circumference <10th percentile, Campbell 1976), a previous anatomy scan at ≤ 20 weeks to confirm dates and with no evidence of fetal abnormality; a gestational age between 24 and 36 completed weeks at recruitment; two normal umbilical artery Doppler studies within the last week (resistance index ≤ 95 th percentile for gestation, Duggan & McCowan 1993), no evidence of oligohydramnios; and provided informed consent to participate in the study.

Oligohydramnios was considered an exclusion criteria as it can be due to reduced renal perfusion and may be a marker of pending fetal hypoxia (Nicolaidis et al 1990). Frequent fetal surveillance is recommended in the SGA fetus with oligohydramnios

(Visser 1995) and randomisation to fortnightly surveillance was therefore not considered appropriate.

Randomisation was by a telephone call to a person not involved in the study, who used computer generated numbers to assign women to either twice weekly or fortnightly tests of fetal surveillance. In those allocated to twice weekly surveillance, it was planned to perform biophysical profile scores, non-stress tests, umbilical and middle cerebral artery Doppler studies twice weekly. Growth scans and uterine artery Doppler studies were performed at fortnightly intervals. In the fortnightly surveillance group it was planned to perform biophysical profile scores, non-stress tests, umbilical, middle cerebral and uterine artery Doppler studies, and growth scans, at fortnightly intervals. If the umbilical artery Doppler resistance index became abnormal during the study further conservative management was not considered appropriate. Women randomised to fortnightly surveillance then received twice weekly surveillance and both groups were offered entry to the concurrent randomised controlled trial to test whether low dose aspirin (100 mg) could increase birthweight, in SGA fetuses with abnormal umbilical artery Doppler studies (chapter 5). The results from women who developed abnormal umbilical artery Doppler results during the study are analysed by intention to treat. It was decided at the outset that subgroup analysis comparing the two regimens of fetal surveillance, would be carried out for women who remained undelivered at ≥ 14 days after randomisation. This would enable evaluation of outcomes in the subgroup who received at least one test of fetal surveillance a fortnight after study entry.

The methodology for the Doppler studies is described in chapter 4. When both middle cerebral and umbilical artery Doppler studies had been performed within two weeks of delivery a ratio of middle cerebral RI/umbilical RI was calculated. An abnormal ratio was <1 (Arias 1994).

The research midwife instructed all women to monitor fetal movements and to keep a kick chart. She met each woman at all hospital visits, conducted the non-stress tests and arranged the scans and biophysical profile testing. Results of all tests were recorded in the notes and the referring obstetrician was contacted if abnormal test results were obtained.

Clinical management was the responsibility of the referring obstetrician and most women had a clinical review with their obstetrician at weekly intervals. Additional tests could be ordered if clinically indicated. Usual hospital practice was to induce labour between 38 and 40 weeks in women with uncomplicated SGA pregnancies.

6.2.2 Outcome Measures

The main outcome measures were markers of newborn morbidity including: gestation at delivery, admission to and duration of stay in the newborn special care unit, duration of newborn hospital stay, acidosis at birth, hypoglycemia, and perinatal deaths. Other outcome measures were maternal interventions including caesarean section, caesarean section for fetal distress, and induction of labour.

6.2.3 Definitions

- Oligohydramnios was present when the vertical depth of the deepest pocket of liquor was ≤ 2 cm (Chamberlain et al 1984).
- Fetal distress in labour was defined as the presence of a suspicious fetal heart pattern for >1 hour or a pathological fetal heart pattern for > 30 minutes (FIGO 1987) and/or a scalp pH <7.25 .
- Babies were routinely admitted to the newborn units if birthweight was <2 kg, gestation <35 weeks, or if they required IV fluids or oxygen. Blood glucose monitoring, incubator therapy, IV antibiotics, and phototherapy were available on the postnatal wards.

6.2.4 Statistical Methods

a) *Sample size*

This randomised trial was carried out concurrently with a randomised trial of low dose aspirin treatment in SGA pregnancies with abnormal Doppler studies (chapter 5).

The sample size had been calculated to have the power to recruit sufficient numbers to the aspirin study.

It was decided pragmatically that the normal Doppler surveillance trial would be a pilot study and would continue until recruitment was completed for the aspirin trial. A sample size was therefore not prespecified. If the results were encouraging the feasibility of obtaining funding for a multicentre trial would be considered. For such a trial, about 1730 women would need to be recruited to each arm to detect a 20% difference in admissions to the newborn special care unit with a background

admission rate estimated at 20% ($\alpha=0.05$, power=80%). A trial of this magnitude is not possible, in a reasonable time period, in our centre.

A retrospective power calculation showed that this study had >99% power to detect an increase in the prevalence of abnormal middle cerebral/umbilical artery resistance index ratio from 10% (background rate in study) to 50% in babies delivered by caesarean section for fetal distress.

b) Statistical analysis

Statistical analysis was carried out using Statview (SAS, Institute 2nd edition 1998) and the SAS system 6.12 statistical package. Data are expressed as mean (SD) or median (range) as appropriate. General statistical methods are described in chapter 4.

6.3 RESULTS

One hundred and sixty seven women were randomised, 85 to twice weekly and 82 to fortnightly surveillance. The group randomised to twice weekly surveillance were younger than the fortnightly group but they did not differ significantly in other background characteristics (table 6.1).

Table 6.1 Background characteristics of the women

	Twice weekly surveillance n=82	Fortnightly surveillance n=85	P value
Gestational age at consent (days)	239 (13)	241 (14)	0.37
Umbilical artery RI at consent	0.64 (0.06)	0.63 (0.06)	0.28
Maternal age (years)	24.3 (5.1)	26.4 (5.5)	0.01
Ethnicity			
European	47 (57%)	52 (61%)	0.07
Maori	17 (21%)	13 (15%)	
Pacific Island	10 (12%)	4 (5%)	
Other	8 (10%)	15 (18%)	
Parity			
0	49 (60%)	43 (51%)	0.56
1	17 (21%)	24 (28%)	
≥2	16 (19%)	18 (21%)	
Smoker	36 (44%)	29 (34%)	0.12

RI = resistance index

Numbers are mean (SD) or number (%) as appropriate

One hundred and four babies (62%) were SGA at birth and 68 (41%) had a ponderal index below the tenth centile (table 6.2). There was a trend to fewer SGA babies in the twice weekly surveillance group ($p=0.06$) and mean gestation at delivery was four days less in this group ($p=0.04$). Six umbilical artery Doppler studies (4%) became

abnormal during the study, five in the twice weekly group and one in the fortnightly group. Fifty four babies (32%) were admitted to the newborn nursery, but rates of admission, duration of stay in hospital and other markers of newborn morbidity, did not differ between groups. There were no perinatal deaths and only two babies (both in the twice weekly group), delivered at 30 and 32 weeks, required ventilation.

Table 6.2: Newborn and maternal outcome

	Twice weekly surveillance n=85	Fortnightly surveillance n=82	P value
Newborn			
Gestational age at delivery (days)	264 (13)	268 (12)	0.04
Umbilical artery RI at delivery	0.63 (0.08)	0.61 (0.06)	0.07
Abnormal umbilical RI at delivery	5 (6%)	1 (1%)	0.21
Female sex	43 (51%)	46 (56%)	0.47
Birthweight (g)	2534 (454)	2587 (412)	0.42
Birthweight < 10th%	47 (55%)	57 (69%)	0.06
Ponderal index	2.42 (0.29)	2.40 (0.28)	0.59
Ponderal index <10th%	29 (34%)	39 (48%)	0.08
Admitted to newborn nursery	26 (31%)	28 (34%)	0.62
Newborn hospital days	5 (0-66)	4 (1-27)	0.10
Acidosis at birth	4 (5%)	3 (4%)	1.0
Hypoglycemia	16 (19%)	18 (22%)	0.62
Maternal			
Spontaneous onset of labour	8 (9%)	21 (26%)	0.006
Induction of labour	70 (82%)	54 (66%)	0.02
Caesarean section	13 (15%)	11 (13%)	0.73
Caesarean section for fetal distress	7 (8%)	7 (9%)	0.94
Preeclampsia	4 (5%)	1 (1%)	0.37
Gestational hypertension	20 (24%)	13 (16%)	0.21

Data are mean (SD), median (range) or number (%) as appropriate

Cord arterial gases were available in 97 (58%) of cases (49 in twice weekly and 48 in fortnightly). Seven babies (three in the twice weekly and four in the fortnightly groups), were acidotic at birth. No baby developed hypoxic ischaemic encephalopathy or meconium aspiration syndrome.

Women in the twice weekly surveillance group were less likely to start labour spontaneously and more likely to be induced than those in the twice weekly group (table 6.2). The caesarean section rate for the whole study group was 14% and did not differ between groups. The caesarean section rate for fetal distress for the study group was 8% (14/167) compared with 5.6% (449/8055) for the hospital population ($p=0.12$). Only one caesarean section for fetal distress was performed prior to the onset of regular contractions. Pregnancy induced hypertension was recognised in 24 (28%) of the twice weekly group and in 14 (17%) of the fortnightly group ($p=0.08$)

One hundred and thirty two women remained in the study for ≥ 14 days and pregnancy outcome was compared according to fetal surveillance regimens in this subgroup (table 6.3). The findings did not differ substantially from those found in the analysis of the whole group. Those randomised to twice weekly surveillance were delivered five days earlier, were again more likely to be induced and less likely to start spontaneous labour.

Table 6.3: Newborn and maternal outcomes for those who remained in the study for ≥ 14 days

	Twice weekly surveillance n=63	Fortnightly surveillance n=69	P value
Newborn			
Gestational age at delivery (days)	267 (11)	272 (9)	0.02
Umbilical artery RI at delivery	0.62 (0.10)	0.62 (0.06)	0.91
Abnormal umbilical RI at delivery	1 (2%)	0	0.48
Female sex	35 (56%)	36 (52%)	0.70
Birthweight (g)	2641 (420)	2693 (391)	0.46
Birthweight < 10th%	37 (59%)	43 (62%)	0.67
Ponderal index	2.45 (0.29)	2.45 (0.28)	0.98
Ponderal index <10th%	21 (33%)	29 (42%)	0.30
Admitted to newborn nursery	14 (22%)	17 (25%)	0.74
Newborn hospital days	5 (0-29)	4 (1-18)	0.15
Acidosis at birth	0	3 (4%)	0.25
Hypoglycemia	10 (17%)	13 (22%)	0.65
Maternal			
Spontaneous onset of labour	5 (8%)	20 (29%)	0.002
Induction of labour	54 (86%)	47 (68%)	0.02
Caesarean section	9 (14%)	7 (10%)	0.47
Caesarean section for fetal distress	5 (8%)	4 (6%)	0.63
Preeclampsia	2 (3%)	0	0.23
Gestational hypertension	15 (24%)	8 (12%)	0.06

Data are mean (SD), median range or number (%) as appropriate

Compliance with the prescribed frequency of fetal surveillance was assessed in all women who remained in the study for ≥ 14 days, excluding the single woman who developed abnormal Doppler studies and underwent subsequent twice weekly surveillance (table 6.3). Compliance was variable in both groups. In the group randomised to twice weekly fetal surveillance the median interval between visits was 4.3 days (range 2-21) but 10 of the 59 (17%) came less often than requested. In the fortnightly group the median interval between visits was 9.3 days (range 3-28), but 37/68 (54%) attended for fetal surveillance more often than fortnightly.

A secondary analysis was performed to determine the prevalence of abnormal uterine and cerebral/umbilical artery resistance index ratios and to determine whether abnormal results were associated with delivery for fetal distress or measures of newborn morbidity. Cerebral/umbilical resistance index ratios were available within two weeks of delivery in 134/167 (80%) of cases. Abnormal results were obtained in 12 (10%), 8/69 (12%) in the twice weekly group and 4/65 (6%) in the fortnightly group. Twelve of the fourteen babies that were delivered by caesarean section for fetal distress had cerebral/umbilical resistance index ratios in the two weeks preceding delivery and all were normal. There was a trend for more newborn admissions in babies with low cerebral/umbilical resistance index ratios [7/12 (58%) admitted with low ratios versus 37/121 (31%) in those with normal ratios $p=0.05$]. Similarly, there was a trend to more hypoglycemia in babies with low cerebral/umbilical resistance index ratios [5/11 (45%) in those with low ratios versus 22/112 (20%) in those with normal ratios $p=0.05$].

Uterine artery Doppler studies were available in 153/167 (92%) and in 52 (34%) cases one or more uterine artery resistance index was abnormal [25/72 (35%) in the twice weekly group and 27/81 (33%) in the fortnightly group]. Thirteen of the fourteen babies delivered by caesarean section for fetal distress had uterine artery Doppler studies and abnormal results were found in four (31%). Babies with abnormal uterine artery Doppler studies were more likely to be admitted to the newborn nursery than those with normal uterine artery Doppler studies [24/52 (46%) versus 25/101 (25%) $p=0.008$] but were not more likely to be hypoglycemic at birth [12/47 (26%) hypoglycemia in those with abnormal uterine artery Doppler studies versus 16/91 (18%) in those with normal uterine artery Doppler studies $p=0.27$].

6.4 DISCUSSION

This pilot randomised controlled trial of two regimens of fetal surveillance, as expected, did not demonstrate any difference in major newborn morbidity between the two study groups. A much larger trial ($n=2000$) would be required to detect a difference in newborn nursery admission, if one indeed exists. Women randomised to twice weekly surveillance were delivered four days earlier and this may be the explanation for the trend to fewer SGA babies in this group. This study does provide important additional data which confirms that serious newborn morbidity is low in SGA pregnancies with normal umbilical artery Doppler studies. There were no perinatal deaths and only two preterm babies required ventilation. Seven babies were mildly acidotic at birth but none of these suffered major complications in the newborn period. Nevertheless, our data suggest that babies born from SGA pregnancies with normal umbilical artery Doppler studies are not merely small normal babies. Thirty two percent were admitted to the newborn nursery, 20% experienced

hypoglycemia and 40% showed evidence of being undernourished, as assessed by low ponderal index at birth.

Eight percent of babies were delivered by caesarean section for fetal distress which is not significantly different from the rate in the total hospital population (5.6%). Only one of the 14 caesarean sections for fetal distress was performed prior to the onset of labour. This suggests that the rate of antenatal fetal compromise is very low in these pregnancies and our results are in keeping with those of a previous report (Bekedam et al 1990).

We also investigated the prevalence of abnormal cerebral/umbilical resistance index ratios and abnormal uterine artery Doppler studies. We evaluated whether these Doppler studies could identify the subgroup of SGA pregnancies, with normal umbilical artery Doppler studies, which developed fetal or newborn morbidity (caesarean delivery for fetal distress, newborn nursery admission, hypoglycemia). A ratio of middle cerebral/umbilical artery resistance ratio has previously been found to be a better predictor of adverse perinatal outcome in SGA fetuses than Doppler indices from either vessel on its own (Arduini & Rizzo 1992). A ratio of <1 has been found to be the best predictor of SGA and newborn morbidity (Arias 1994). In our study only 10% of cerebral / umbilical resistance ratios recorded within two weeks preceding delivery were abnormal. These results suggest that in SGA fetuses with normal umbilical artery Doppler studies redistribution of fetal cardiac output to the extent measured by abnormal cerebral / umbilical resistance ratios is uncommon. These abnormal (low) ratios were not more common in the babies delivered by caesarean section for fetal distress. However abnormal ratios were associated with

a trend to more newborn nursery admissions and to newborn hypoglycemia. The utility of this ratio in the subgroup of SGA fetuses with normal umbilical artery Doppler studies has only been addressed indirectly in one previous publication (Strigini et al 1997). In this study, if umbilical artery Doppler results were normal, cerebral Doppler assessment did not improve the prediction of adverse perinatal outcome.

Uterine artery Doppler studies were abnormal in one third of cases. Abnormal uterine artery Doppler studies were not more common in pregnancies delivered by caesarean section for fetal distress but babies requiring newborn admission were twice as likely to have abnormal uterine artery Doppler studies. Abnormal uterine artery Doppler studies have been associated with placental bed biopsies demonstrating defective trophoblast replacement of the spiral arteries (Lin et al 1995). The finding of abnormal uterine artery Doppler studies in one third of SGA pregnancies, with normal umbilical artery Doppler studies, again suggests that these are not just small normal pregnancies. Further studies will be necessary to confirm whether abnormal uterine artery Doppler studies in this context can predict babies more likely to experience problems in the newborn period.

As far as maternal morbidity was concerned women who were randomised to twice weekly surveillance were more likely to be induced and less likely to start spontaneous labour. This suggests that more frequent hospital attendance may result in more medical intervention. The twice weekly group also had a trend to more diagnoses of hypertension which is again not surprising considering their more frequent hospital attendance. Further studies will be necessary to determine whether

the earlier delivery which was associated with more frequent surveillance is also associated with a lower risk of SGA at birth.

In the women randomised to fortnightly surveillance the median interval between visits (9.3 days) was more than twice that in the women randomised to twice weekly surveillance (4.3 days). However, over half of the women randomised to fortnightly surveillance attended for additional tests of fetal wellbeing. As these extra tests of fetal wellbeing were ordered by a clinician it suggests that the clinicians were not always comfortable with the planned reduced frequency of fetal surveillance. It also makes it difficult to assess whether the apparent safety of planned fortnightly monitoring may have been due in part to this additional surveillance. Thus future trials assessing the safety of less frequent surveillance will need to take this into account.

As this study piloted a trial to test for differences in two treatment regimens it is important to assess sample size requirements for any full study that may ensue. The original sample size estimate, in the order of 1700 per group, to detect a 20% increase in the rate of newborn nursery admission was based on a predicted admission rate of 20%. However in this study the admission rate was 32%. To detect a 20% increase in admission rate from 32% to 38% about 1000 are needed in each group. An even larger sample size would be required to detect a 20% increase in the prevalence of acidosis at birth from 5% to 6% (about 8,300 in each group). The current study had sufficient power to detect a 20% difference in the rate of spontaneous labour between groups with the twice weekly group having a background rate of about 10%.

6.5 SUMMARY

In this study of SGA pregnancies with normal umbilical artery Doppler studies, low rates of newborn morbidity were found, whether antenatal surveillance was undertaken at planned fortnightly or planned twice weekly intervals. Maternal intervention (induction of labour) was more common in the twice weekly surveillance group. However the study did not have the power to detect clinically important differences in newborn outcomes or in caesarean section rates. Additional surveillance was also commonly ordered by clinicians in the planned fortnightly surveillance group. Further large clinical trials are required to determine the safety and potential benefits of less frequent surveillance in SGA pregnancies with normal umbilical artery Doppler studies. Such trials will need to include carefully defined criteria for surveillance additional to that planned at randomisation. Primary outcome measures should include evidence of morbidity for mother and baby and economic analysis should also be considered.

Further studies are necessary to determine whether cerebral or uterine artery Doppler studies can predict the subgroup of SGA pregnancies with normal umbilical artery Doppler studies that experience newborn morbidity.

CHAPTER 7

PERINATAL OUTCOME IN SMALL FOR GESTATIONAL AGE BABIES IN RELATION TO UMBILICAL ARTERY DOPPLER STUDIES

7.1 INTRODUCTION

Umbilical artery Doppler studies appear to enable the classification of small for gestational age babies into groups with varying degrees of risk to the fetus and newborn (Reuwer et al 1987, Burke et al 1990, Trudinger et al 1991, Snijders et al 1997). Those with abnormal umbilical artery Doppler studies have histological evidence of placental vascular pathology (Giles et al 1985, McCowan et al 1987, Krebs et al 1996) and are at increased risk of perinatal death, iatrogenic preterm delivery and morbidity in the newborn period (Burke et al 1990, Trudinger et al 1991, Soothill et al 1993, Gaziano et al 1994). Few investigators have examined the potential confounding effects, of gestational age at delivery (Trudinger et al 1991, Yoon et al 1994) and / or the severity of growth restriction on perinatal outcome (Trudinger et al 1991). There are no reports of perinatal outcome in relation to umbilical artery Doppler status which have controlled for birthweight. There are also no previous published reports of markers of newborn malnutrition in SGA babies in relation to umbilical artery Doppler studies.

In contrast with SGA babies with abnormal umbilical artery Doppler studies, those with normal umbilical artery Doppler studies are unlikely to be stillborn or to experience major complications during pregnancy or the neonatal period (Burke et al

1990, Trudinger et al 1991, Gaziano et al 1994). Several authors have therefore described these babies as being normal, constitutionally small babies (Burke et al 1990, James et al 1992, Soothill et al 1993). If these babies are normal but constitutionally small then their mothers should also be small. One would also expect that they would rarely require admission to the newborn nursery, show evidence of being malnourished at birth, or experience neonatal problems such as hypoglycemia.

We therefore wished to test the following hypotheses;

- 1) Abnormal umbilical artery Doppler studies would be associated with newborn morbidity in SGA babies independent of birthweight and gestational age.
- 2) In SGA babies with normal umbilical artery Doppler studies, newborn morbidity and evidence of malnutrition would be less common than in SGA babies with abnormal umbilical artery Doppler studies.
- 3) The rate of admission to the newborn nursery in SGA babies with normal Doppler studies would not differ to that in the general hospital population.
- 4) Mothers of SGA babies with normal umbilical artery Doppler studies would be lighter, shorter, and of different ethnic distribution than those with abnormal Doppler studies.
- 5) Mothers of SGA babies with abnormal umbilical artery Doppler studies would have a higher incidence of vascular disorders during pregnancy.

7.2 METHODS

7.2.1 General

The subjects in this study were the women and their babies who took part in one of the two randomised controlled trials in SGA pregnancies (chapters 5 & 6) and after birth were confirmed to have SGA babies (birthweight <10th percentile, Guaran et al 1994). Those with abnormal umbilical artery Doppler studies were randomised to a trial of low dose aspirin or placebo (chapter 5) and received at least twice weekly tests of fetal surveillance. Those with normal umbilical artery Doppler studies were randomised to either twice weekly or fortnightly regimens of fetal surveillance (chapter 6).

Study babies were routinely admitted to the newborn units if birthweight was <2kg, gestation <35 weeks, or if they required IV fluids or oxygen. Blood glucose monitoring, incubator therapy, IV antibiotics, and phototherapy were available in the postnatal wards.

Standard deviation (z) scores were calculated for birthweight, length and head circumference, as the difference between the actual measurement and population mean measurement for gestational age divided by the standard deviation, based upon Melbourne birth standards (Guaran et al 1994). This method allows direct comparison of infant measurements independent of gestational age. For example, a baby with birthweight one standard deviation below the mean at any gestational age has a weight z-score of -1.

7.2.2 Statistical Methods

a) *Sample size calculation*

A prospective sample size calculation was not done for this study. The number of subjects available was determined by the sample size necessary for the randomised controlled trial of low dose aspirin in SGA fetuses with abnormal umbilical artery Doppler studies (chapter 5).

A retrospective power calculation demonstrated that this study had > 99% power to detect an increase in the rate of admission to the newborn nursery from 35% (admission rate for SGA with normal Doppler) to 75% (admission rate in abnormal Doppler group) with 60 SGA babies required in the normal Doppler group and 30 in the abnormal group.

b) *Statistical analysis*

Statistical analysis was carried out using Statview (SAS Institute, 2nd edition 1998) and the SAS system 6.12 statistical package. Values are expressed as mean (SD) for normally distributed data, and median (10th, 90th percentiles) where data are not normally distributed. Relative risks or Fishers exact test were used for comparisons between groups as appropriate. Logistic regression analysis was used to determine whether the results of umbilical artery Doppler studies added significant information over that provided by birthweight and gestational age at delivery, for the prediction of admission to the newborn nursery and hypoglycemia. Birthweight and gestational age at delivery were selected as variables for logistic regression as each was associated with the above measures of newborn morbidity in univariate analysis. Logistic regression was also used to compare rates of admission to the newborn

nursery between the total hospital population and SGA babies with normal umbilical artery Doppler studies.

7.3 RESULTS

7.3.1 General

Two hundred and sixty nine pregnancies in which the fetus was suspected to be SGA were enrolled in the two randomised controlled trials.

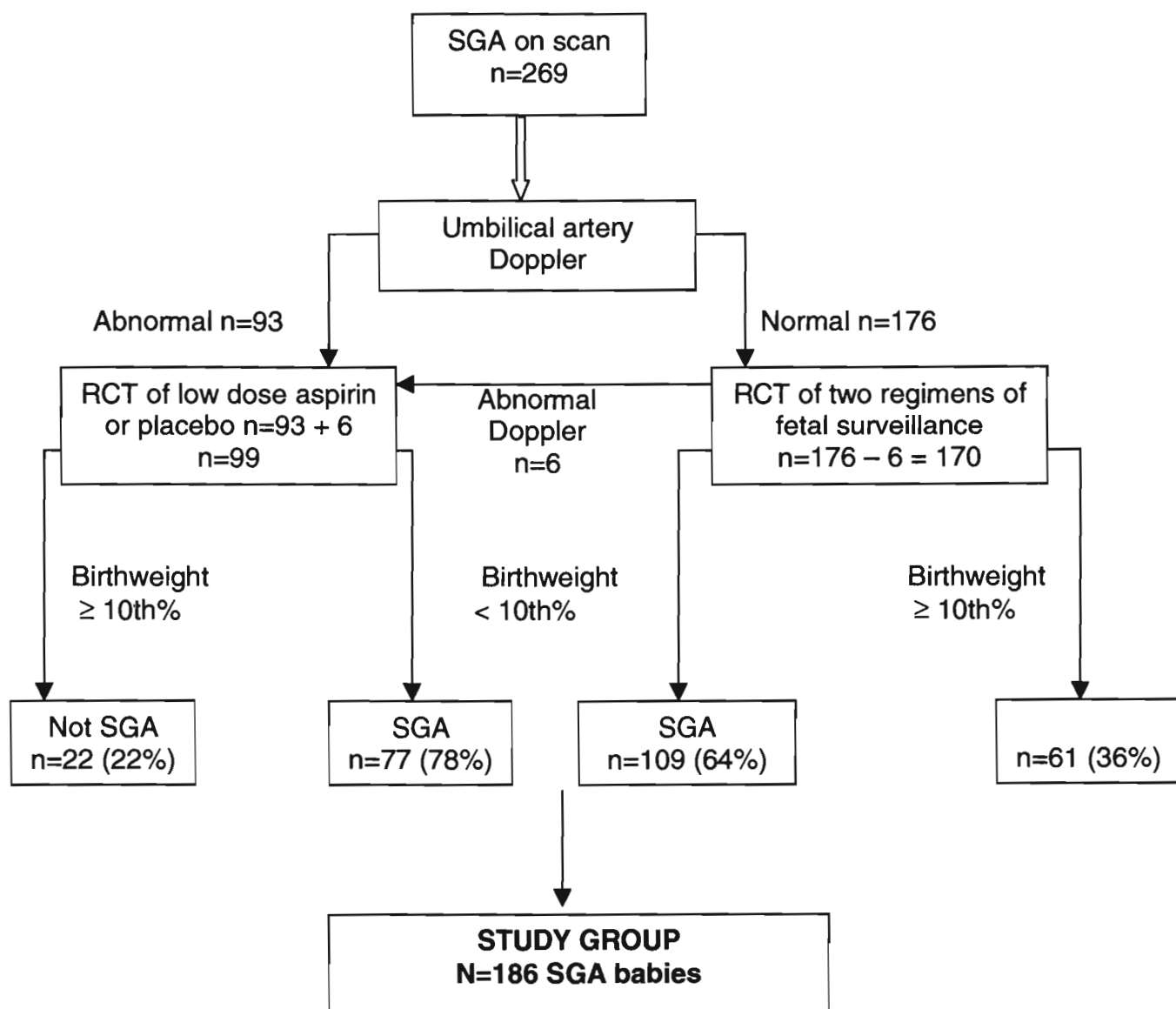


Figure 7.1 Study Population

At the time of randomisation 93 (35%) had abnormal and 176 (65%) had normal umbilical artery Doppler studies (fig 7.1). In six cases initial recruitment was to the normal Doppler study, however these women were subsequently enrolled in the abnormal Doppler study when umbilical artery Doppler results became abnormal. They are included with the abnormal Doppler group for the purposes of this report. Nine women in the normal Doppler group had a gestational age at recruitment, to the normal Doppler trial of fetal surveillance, of >36 weeks. They were therefore excluded from the former analysis but their data are included in this report.

Seventy seven (78%) of babies with abnormal umbilical artery Doppler studies were SGA at birth compared with 109 (64%) in the normal Doppler group ($p=0.007$). These 186 SGA babies and their mothers comprise the study group.

7.3.2 Fetal and Newborn Characteristics

SGA babies with abnormal umbilical artery Doppler studies were identified to be small by ultrasound scan (abdominal circumference <10th percentile, Campbell 1976) earlier in pregnancy than those with normal umbilical artery Doppler studies [30.3 (3.3) weeks versus 32.9 (6.2) weeks, $p < 0.001$]. They were also assessed as smaller on the last ultrasound scan before delivery as indicated by a ratio of measured abdominal circumference/mean abdominal circumference for gestation [0.82 (0.06) versus 0.87 (0.03) $p=0.0001$].

SGA babies with abnormal umbilical artery Doppler studies were born nearly three weeks earlier and were smaller in all body proportions than those with normal

umbilical artery Doppler studies even allowing for their earlier gestational age at delivery (table 7.1). However they were not more likely to have a low ponderal index.

Table 7.1: Neonatal morphometry

	Abnormal Doppler	Normal Doppler	P value or
	n=77	n=109	RR (95% CI)
Gestation at delivery(weeks)	35.8 (29.3, 38.3)	38.1 (36.3, 40.1)	<0.0001
Birthweight (gm)	1700 (653, 2552)	2435 (2074, 2818)	<0.0001
z score birthweight	-1.8 (-2.9,-1.3)	-1.6 (-2.3, -1.2)	0.002
Length (cm)	43.0 (32.0, 47.5)	47.2 (44.2, 49.0)	<0.0001
Length <10th%	61/74 (82%)	50/109 (46%)	1.8 (1.4-2.3)
z score length	-1.86 (-3.56, -0.96)	-1.36 (-2.25, -0.28)	<0.0001
HC (cm)	30.5 (23.2,33.0)	33.0 (31.0, 34.5)	<0.0001
HC <10th%	37/75 (49%)	24/109 (22%)	2.2 (1.5-3.4)
z score HC	-1.3 (-2.5, -0.6)	-0.9 (-2.1, 0.1)	<0.0001
Ponderal index	2.2 (1.9, 2.6)	2.4 (2.1, 2.7)	<0.0001
Ponderal index <10th%	27/74 (36%)	53/109 (49%)	0.8 (0.5-1.0)
Placental weight	325 (114)	438 (119)	<0.0001
Female	47 (61%)	65 (60%)	1.0 (0.8-1.3)

HC = head circumference

Data are number (%), median (10th, 90th centiles), or mean (SD) as appropriate

Babies with abnormal umbilical artery Doppler studies were twice as likely to be admitted to the newborn nursery and spent longer in hospital (table 7.2). However

when birthweight, gestational age at delivery and umbilical artery Doppler status were entered into a logistic regression model to determine the factors important in admission to the newborn nursery, birthweight [OR 7.3 (95% CI 2.2-25) for each standard deviation of birthweight below the mean] and gestation at delivery [OR 12.7 (95% CI 5.5-28.6) for delivery at <37 weeks], had significant independent effects. The effect of abnormal umbilical artery Doppler was no longer significant. The rates of newborn nursery admission, by gestation at delivery in SGA babies, according to umbilical artery Doppler group did not differ and are shown in figure 7.2. Babies with abnormal umbilical artery Doppler studies were also more likely to experience hypoglycemia after birth. However when birthweight, gestational age at delivery and Doppler status were entered into a logistic regression model, hypoglycemia was found to be dependent on birthweight (Chi-square 14.4 $p < 0.0001$) and Doppler group did not have a significant effect. This study did not have sufficient power to determine whether Doppler group had an independent effect on perinatal death.

Table 7.2: Neonatal morbidity

	Abnormal Doppler	Normal Doppler	P value or
	n=77	n=109	RR (95% CI)
Admitted to newborn nursery	57 (74%)	38 (35%)	2.1 (1.6-2.8)
Days in newborn nursery	15 (0,68)	0 (0, 11)	<0.0001
Days in hospital	18 (4,74)	5 (2,15)	<0.0001
Perinatal death	7 (9%)	0	0.002
Periventricular haemorrhage	2/63 (3%)	1/78 (1%)	2.5 (0.2-26.7)
Asphyxia	7 (9%)	3 (3%)	3.3 (0.9-12.4)
Hypoglycemia	35/75 (47%)	26/98 (26%)	1.8 (1.2-2.7)
Major congenital or chromosomal abnormalities	2 (4%)	0	0.17

Values are number (%), median (10th,90th centile) as appropriate

In this study there were seven perinatal deaths, all in babies with abnormal umbilical artery Doppler studies (perinatal mortality rate 90/1000). Five of the six deaths (two stillbirths and three neonatal deaths) occurred in babies of borderline viability (birthweights 420 to 570 gm). All of these had very abnormal umbilical artery Doppler studies (last resistance index 0.90 to 1). One baby (birthweight 1405g) died of congenital heart disease in the newborn period and one baby (birthweight 2380g) was stillborn as a result of a placental abruption.

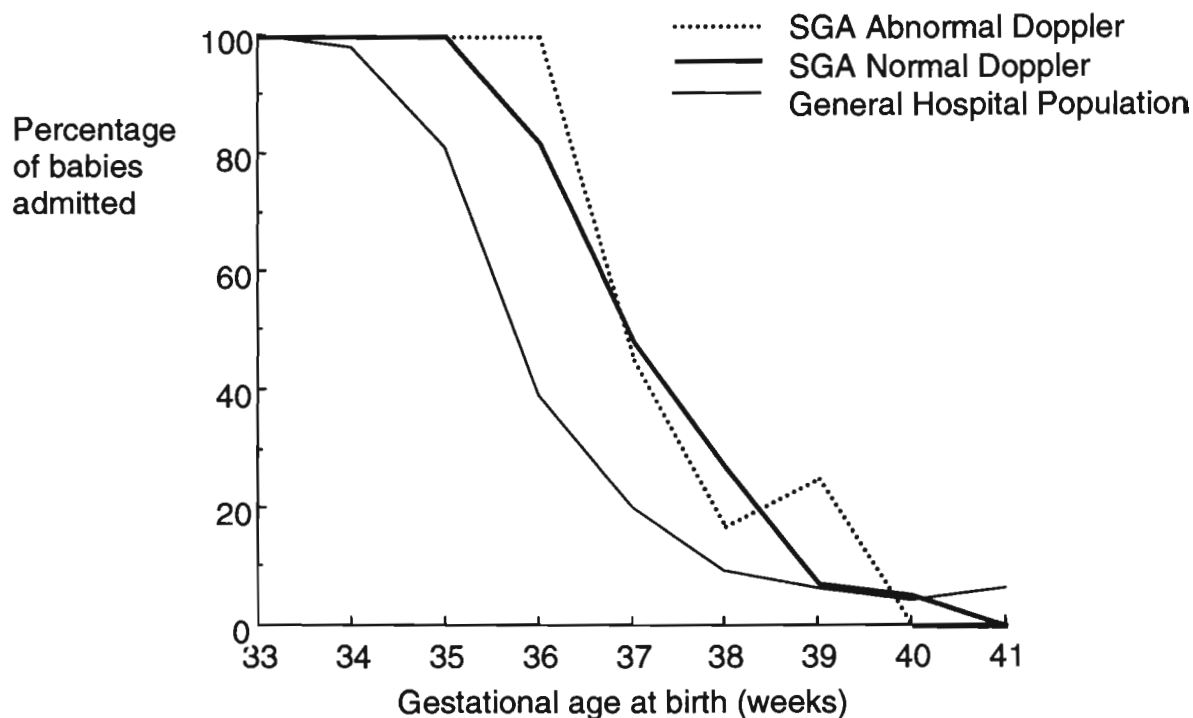


Figure 7.2 Newborn nursery admissions for total hospital births compared with SGA babies according to umbilical artery Doppler studies

The rates of admission to the newborn nursery have been compared between the hospital population and SGA babies with normal umbilical artery Doppler studies, analysed according to gestation at delivery (figure 7.2). SGA babies with normal umbilical artery Doppler studies overall had a higher rate of admission 38/109 (35%) compared with 956/7665 (12%) in the general hospital population (Chi-square=26, degrees of freedom=1, $p < 0.0001$). The odds of SGA babies with normal umbilical artery Doppler studies being admitted to the newborn nursery was 1.8 times that of babies in the hospital population.

7.3.3 Maternal Characteristics

No difference was found in maternal height, weight or ethnicity (table 7.3) between mothers of SGA babies with normal versus abnormal umbilical artery Doppler studies. However mothers of SGA babies with abnormal umbilical artery Doppler studies were older and of different parity distribution than those of SGA babies with normal umbilical artery Doppler studies.

Table 7.3: Maternal characteristics

	Abnormal Doppler n=77	Normal Doppler n=109	P value
Age (years)	28.3 (6.0)	25.6 (5.4)	0.002
Parity			
0	38 (49%)	64 (59%)	0.03
1	29 (38%)	24 (22%)	
≥2	10 (13%)	21 (19%)	
Height (cm)	161.5 (6.0)	162 (7.3)	0.68
Booking weight (kg)	62.8 (14.5)	60.7 (11.6)	0.34
Ethnic group			
European	54 (70%)	67 (62%)	0.37
Maori	7 (9%)	20 (18%)	
Pacific Island	3 (4%)	6 (6%)	
Asian	11 (14%)	11 (10%)	
Other	2 (3%)	4 (4%)	
Number of cigarettes smoked per day			
0	44 (57%)	63 (58%)	0.92
1-10	18 (23%)	27 (25%)	
≥11	15 (20%)	19 (17%)	

Values are mean (SD), number (%) as appropriate

Mothers of SGA babies with abnormal umbilical artery Doppler studies were more likely to have experienced previous pregnancy complications but these differences were not statistically significant (table 7.4). They had a trend to more underlying vascular problems and were twice as likely to have evidence of abnormal uteroplacental perfusion as assessed by abnormal uterine artery Doppler studies. They had higher mean systolic blood pressure in the first half of pregnancy, and were more likely to go on to develop preeclampsia. However mothers of SGA babies with normal umbilical artery Doppler studies also had a high (20%) incidence of gestational hypertension. In 33/63 (52%) cases of pregnancy induced hypertension, the hypertension was recognised after the initial diagnosis of SGA was made [24/38 (63%) in the abnormal umbilical artery Doppler group and 9/25 (36%) in the normal umbilical artery Doppler group].

Table 7.4: Maternal complications in past and current pregnancy

	Abnormal Doppler n=77	Normal Doppler n=109	P value
Previous pregnancy			
Previous SGA baby ¹	23/39 (59%)	22/45 (49%)	0.35
Previous preeclampsia ¹	7/39 (18%)	3/45 (7%)	0.10
Previous perinatal death ¹	4/39 (10%)	1/45 (2%)	0.15
Current pregnancy			
Maternal vascular disease ²	8 (10%)	4 (4%)	0.06
Abnormal uterine artery Doppler	45/77 (58%)	32/107 (30%)	<0.0001
Maximum systolic BP < 20 wks	115 (15)	109 (15)	0.004
Maximum diastolic BP <20 wks	68 (11)	67 (10)	0.44
Gestational hypertension	21 (27%)	22 (20%)	0.25
Preeclampsia	17 (22%)	3 (3%)	<0.0001
Antepartum haemorrhage	3 (4%)	9 (8%)	0.36

¹ denominator=women with parity ≥ 1 ;

² maternal vascular disease=chronic hypertension, renal disease, lupus anticoagulant, anticardiolipin antibody; Values are mean (SD), number (%) as appropriate

Mothers of SGA babies with abnormal umbilical artery Doppler studies were more likely to be delivered by caesarean section, were more likely to require caesarean section for fetal distress and were less likely to be induced than those with normal Doppler studies (table 7.5).

Table 7.5: Maternal birth outcomes

	Abnormal Doppler	Normal Doppler	RR (95% CI)
	n=77	n=109	
Spontaneous labour	2 (3%)	12 (11%)	0.24 (0.05-1.02)
Induction of labour	46 (60%)	87 (80%)	0.75 (0.61-0.92)
Caesarean section	40 (51%)	17 (16%)	3.33 (2.05-5.42)
Caesarean section for fetal distress	22 (29%)	10 (9%)	3.11 (1.56-6.20)

Values are number (%)

7.4 DISCUSSION

As has been shown by others (Reuwer et al 1987, Trudinger et al 1991, James et al 1992) perinatal morbidity and mortality were significantly greater in SGA babies with abnormal umbilical artery Doppler studies than in those with normal studies. When birthweight, gestational age at delivery and umbilical artery Doppler status were entered into a logistic regression model to determine the factors independently contributing to admission to the newborn nursery, birthweight and gestation at delivery had a significant effect but abnormal umbilical artery Doppler did not. Similarly, hypoglycemia at birth was independently associated with birthweight but not with umbilical artery Doppler group.

Previous studies comparing perinatal outcome in relation to umbilical artery Doppler studies have not considered the confounding effects of birthweight as well as gestational age at delivery (Rochelson et al 1987, Gaziano et al 1994). In a large study of neonatal outcome in relation to umbilical artery Doppler findings by

Trudinger et al (1991), when babies were grouped by gestational age at delivery, those with abnormal Doppler studies spent significantly longer in the neonatal intensive care unit. In a study of the role of umbilical artery Doppler in predicting adverse perinatal outcome in women with preeclampsia, Yoon et al (1994) reported that when gestational age at birth and preeclampsia were controlled for, abnormal umbilical artery Doppler was still a significant independent predictor of adverse perinatal outcome. However neither of these earlier studies controlled for birthweight in their statistical analyses.

The presence of abnormal umbilical artery Doppler studies was associated with more severe SGA in utero as indicated by abdominal circumference measurements further below the mean before delivery, and also earlier antenatal recognition of the SGA on scan. This finding of more severe SGA was also confirmed after birth and was independent of gestational age, as z score measurements for birthweight, head circumference and length were all further deviated from the mean in babies with abnormal as compared with normal umbilical artery Doppler studies. Abnormal umbilical artery Doppler is therefore a marker of a more severe disease process in the SGA baby. The degree of growth restriction in SGA babies in relation to umbilical artery Doppler findings, has not been addressed in detail before. A number of studies have found that SGA babies with abnormal umbilical artery Doppler studies are smaller and delivered earlier than those with normal umbilical artery Doppler studies (Burke et al 1990, Trudinger et al 1991, James et al 1994). Only one previous study (Trudinger et al 1991) has reported on the degree of growth restriction in relation to umbilical artery Doppler. In this large study (n=2178) of high risk pregnancies, abnormal Doppler studies were associated with a lower mean

birthweight centile and more babies with birthweight <10th percentile. Only 30% of babies in that study were SGA at birth, but the results are consistent with ours. One other study has reported on the relationship between the degree of abnormality of aortic Doppler waveforms and the degree of growth restriction (Ley et al 1996¹, Ley et al 1996²). Birthweight deviation from the mean increased as aortic Doppler waveforms became more abnormal, consistent with our results.

Ponderal index at birth has been claimed to be independent of race and sex (Walther & Ramaekers 1982) and to be a better marker of newborn morbidity than weight for gestational age (Walther & Ramaekers 1982, Patterson & Pouliot 1987). Ponderal index results have not previously been reported in SGA babies in relation to umbilical artery Doppler studies. We had expected to find more abnormal ponderal indices in the babies with abnormal umbilical artery Doppler studies. The lower prevalence of abnormal ponderal indices in these babies (36% versus 49% in those with normal umbilical artery Doppler studies) is a reflection of the fact that most (82%) with abnormal Doppler studies were short at birth. This may result from the greater severity and/or longer duration of their growth restriction.

There were no perinatal deaths in SGA babies with normal umbilical artery Doppler studies in this series. Among these babies, with a median gestation at delivery of 38 weeks, one third were admitted to the newborn nursery. The odds of SGA babies with normal umbilical artery Doppler studies being admitted to the newborn nursery was 1.8 times that of babies in the hospital population. One quarter were hypoglycaemic, and half had ponderal indices below the 10th percentile, again suggesting that SGA babies with normal umbilical artery Doppler studies are not all

just normal small babies. It has been shown previously in a mathematical model, that 60% or more of terminal placental arterial vessels have to be obliterated before a marked increase occurs in umbilical artery Doppler resistance indices (Thompson et al 1990). In that study larger placentae required more vessel obliteration to achieve an increase in resistance. It is therefore feasible that a proportion of mature SGA babies, with relatively large placentae, could have vascular pathology and still have a resistance index within the normal range for gestation.

This is the first study to report in detail the background characteristics of mothers of SGA babies in relation to umbilical artery Doppler studies. If SGA babies with normal umbilical artery Doppler studies were constitutionally small (due to genetic or racial factors) in relation to SGA babies with abnormal Doppler studies, their mothers might be expected to be smaller and/or of different ethnic distribution compared with mothers of SGA babies with abnormal umbilical artery Doppler studies. However we were not able to detect any difference in maternal size (height, pregnancy booking weight) or ethnic distribution between the two groups.

Mothers of babies with abnormal umbilical artery Doppler studies had more underlying vascular problems. They had higher mean systolic blood pressure at <20 weeks gestation and were more likely to develop preeclampsia than those in the normal Doppler group. Our results are in keeping with those of Rochelson et al (1987) who found that 50% of mothers of SGA babies with abnormal umbilical artery Doppler studies had pregnancy induced hypertension compared with 17% of the mothers of SGA babies with normal umbilical artery Doppler studies. In our study the hypertensive disorder presented after the initial diagnosis of the SGA, in over fifty

percent of cases. This provides support for a common underlying uterine vascular lesion (Khong et al 1986) and also suggests that guidelines for management of SGA should include recommendations for regular monitoring for signs of preeclampsia in the mother. Mothers of babies with abnormal umbilical artery Doppler studies were twice as likely to have abnormal uterine artery Doppler studies than mothers of babies with normal umbilical artery Doppler studies. Idiopathic fetal growth restriction and preeclampsia are both associated with histologic evidence of defective trophoblast invasion of the spiral arteries in the placental bed (Khong et al 1986). Abnormal uterine artery Doppler studies have been correlated with these same histological abnormalities (Voigt & Becker 1992, Lin et al 1995) and therefore reflect uteroplacental vascular pathology.

7.5 SUMMARY

SGA babies with abnormal umbilical artery Doppler studies had earlier onset and more severe SGA. They were born earlier and were smaller at birth than those with normal Doppler studies. However when birthweight and gestational age at delivery were controlled for abnormal umbilical artery Doppler was not an independent predictor of newborn nursery admission or hypoglycemia. SGA babies with normal umbilical artery Doppler studies were not found to be just small normal babies. Their mothers were not small, and nearly one third had evidence of abnormal uteroplacental perfusion. They had high rates of low ponderal index at birth, hypoglycemia and admission to the newborn nursery. Hypertensive disorders in pregnancy and abnormal uterine artery Doppler studies were more common in mothers of SGA babies with abnormal umbilical artery Doppler studies.

It is concluded that umbilical artery Doppler studies reflect disease severity in SGA babies and are not independently associated with neonatal outcome.

CHAPTER 8

PERINATAL PREDICTORS OF SIZE AND GROWTH AT SIX MONTHS IN SMALL FOR GESTATIONAL AGE BABIES

8.1 INTRODUCTION

Children who were small for gestational age at birth are more likely to remain short or to be underweight at two years of age than children who were appropriately grown at birth (Tenovuo et al 1987). Previous studies have shown that between eight and 29% of these SGA babies fail to catch up in height by two years of age (Fitzhardinge & Inwood 1989, Albertsson-Wikland et al 1993, Hokken-Koelega et al 1995, Leger et al 1997) and a similar proportion are still underweight (Fitzhardinge & Inwood 1989, Albertsson-Wikland et al 1993, Leger et al 1997). Poor postnatal growth and persisting short stature may be important for a number of reasons. Children who were SGA at birth and fail to show catch up growth have been found to have a greater likelihood of abnormal neurodevelopmental testing at four years of age (Fancourt et al 1976). Short children are also more likely to underachieve at school even when their intelligence quotient is within the normal range (Law 1987). Adverse effects on psychological and social wellbeing and a high prevalence of behavioural disorders have also been reported in short children (Law 1987). Furthermore, persistent poor growth postnatally has been associated with an increased risk of later hypertension (Barker et al 1989).

Postnatal catch up growth in length occurs at a slower rate than catch up growth in weight. Several investigators have shown that almost all SGA babies who

experience catch up growth in weight will do so by six months of age (Fitzhardinge & Inwood 1989). However about 10% demonstrate continued catch up growth in length after this time (Fitzhardinge & Inwood 1989) continuing up until two (Tenovuo et al 1987, Fitzhardinge & Inwood 1989, Leger et al 1997) to four years of age (Albertsson-Wikland et al 1993). The most rapid velocity in postnatal head growth also occurs in the first six months (Tenovuo et al 1987) and this increase in head circumference correlates well with brain growth (Winick & Rosso 1969). The majority of babies who have failed to demonstrate catch up growth by six months of age will therefore remain small children.

Early identification of children who will remain small may enable earlier interventions aimed at improving later outcomes (Stanhope et al 1991, Castillo Duran et al 1995). At present there is little published information to enable early identification of these children. Only one previous study reported the influence of the gestation of onset of growth restriction in utero on later growth (Fancourt et al 1976). In this study children diagnosed SGA by ultrasound scan at <34 weeks gestation were more likely to be underweight, short or have small head circumferences at four years. Similarly, there are only two reports of the relationship between antenatal Doppler studies and later growth. Neither fetal aortic Doppler waveforms (Marsal et al 1998) nor cerebral/umbilical resistance index ratios were found to predict postnatal growth (Yoshimura et al 1998). Three studies have reported a relationship between the degree of growth restriction at birth, as assessed by SDS in length or weight at two years (Hokken-Koelega et al 1995, Leger et al 1997), and growth at seven years (Marsal et al 1998).

As babies who are small at six months are likely to remain small in later childhood we chose to investigate the perinatal factors associated with short length, low weight, and low head circumference at six months of age.

We tested the hypotheses that children who are small at six months will;

- 1) have been diagnosed as SGA at an earlier stage in pregnancy
- 2) be more likely to have had abnormal umbilical artery Doppler studies before birth
- 3) have had smaller body proportions at birth as measured by z scores for weight, length, and head circumference
- 4) be more likely to have had a normal ponderal index at birth

8.2 METHODS

8.2.1 General

Babies from singleton pregnancies who were SGA at birth (birthweight <10th percentile (Guaran et al 1994)) were eligible to enter the study if: they had a scan at ≤ 20 weeks to confirm gestation, were diagnosed SGA in pregnancy, they had an umbilical artery Doppler study within two weeks of delivery, and if there was no suspicion of chromosomal or congenital abnormality after birth. If the estimated date of delivery calculated from menstrual dates differed from that calculated by scan by more than 10 days, the scan estimated date of delivery was used (Gardosi et al 1997).

In all cases details of the perinatal history, antenatal Doppler studies, newborn morbidity and morphometry, were recorded by the research midwife. The gestation at which the abdominal circumference was first recognised to be <10th percentile, on

ultrasound scan, was the gestation of initial diagnosis of SGA. Babies were measured by the research midwife within 48 hours of birth. When this study started in 1993 local sex specific birth measurement centile charts were not available. Eligibility for the study was therefore determined on the basis of birthweight <10th percentile (Guaran et al 1994) using centile charts which were not sex specific. After the local sex specific centile charts were published (Beeby et al 1996) it was decided to use these to calculate standard deviation (z) scores of birth measurements to reduce the chance of overestimating the severity of growth restriction in male babies.

Babies were measured by the research midwife at three monthly intervals beginning at three months corrected age (i.e three months post term) and continuing until 24 months of age. This followup is ongoing. For the six month growth assessment, babies' weight was measured, without clothes, to the nearest gram using Wedderburn Digital Baby Scales (Tanita Corporation, Tokyo, Japan). Length was measured supine, to the nearest mm, in a neonatometer, and head circumference (maximum occipito-parietal diameter) was measured to the nearest mm. New Zealand sex specific postnatal centile charts (Binney et al 1991) were used to calculate z scores postnatally.

For infants who had their six month assessment performed at a corrected age of less than five months 15 days or greater than six months 15 days, z scores were calculated for the actual post term age and then used to calculate measurements for corrected age which were used for the purposes of data analysis.

Infants were classified as short, underweight, or having a low head circumference if their corrected length, weight or head circumference was less than the population 10th percentile (Binney et al 1991). Children with both length and weight <10th percentile were described as overall small.

There are at least two possible reasons why children who are small at birth may not attain measurements above the 10th percentile by six months of age. Firstly, they may be growing slowly, or secondly, they may be growing rapidly (catchup growth) but still not have reached the 10th percentile because their birth size was so far below the 10th percentile. In order to distinguish between these possibilities the difference in z scores (Δz score) was calculated (Δz score = z score at six months minus z score at birth). A negative Δz score was defined as abnormal indicating failure of catchup growth as the z score was further deviated from the mean between birth and six months of age.

8.2.2 Statistical Methods

Statistical analysis was carried out using Statview (SAS Institute, 2nd edition 1998). Values are expressed as mean (SD), or median (10th, 90th percentiles) as appropriate. Multiple logistic regression analysis was used to determine which variables contributed significantly to being short, underweight, having a small head circumference, or being overall small (short and underweight) at six months. The variables which were found to have a significant effect on these outcomes in univariate analysis were entered into the logistic regression models.

8.3 RESULTS

8.3.1 General

Two hundred and forty eight SGA babies were recruited to this study, of whom 111 (45%) had participated in one of two antenatal randomised controlled trials in SGA pregnancies (chapter 5 & 6) and 137 (55%) were recruited for the first time postnatally. Of the 248 babies who entered the study, all completed followup at three months and 203 (82%) completed followup at six months of age. The mothers of the babies who were lost to followup at six months (n=45) tended to be younger and more likely to smoke than the mothers of babies who completed followup (table 8.1). The babies who were lost to followup at six months were longer at birth and had larger heads than those who were followed up at six months. They also tended to be longer and to have larger heads at three months.

All babies who completed followup to six months (n=203) had their weight measured and length and head circumference measurements were available in 202 babies. Babies were categorised into groups according to whether their length, weight or head circumference were normal or abnormal. Forty (20%) babies were short, 31 (16%) were underweight, 37 (18%) had a small head circumference and 22 (11%) were overall small (short and underweight) at six months.

Table 8.1 Characteristics of those lost to followup between three and six months compared to those who were followed up at six months

	Lost to followup n=45	Followup at six months n=203	P value
Maternal			
Age (yrs)	26.9 (7.5)	28.9 (5.9)	0.05
European ethnicity	27 (60%)	145 (71%)	0.20
Nulliparous	29 (64%)	105 (52%)	0.15
Smoker	19/44 (43%)	57/202 (28%)	0.05
Fetal & Newborn Variables			
Gestation AC <10th% (weeks)	33.3 (3.8)	33.0 (3.6)	0.61
Abnormal umbilical artery	14 (31%)	87 (43%)	0.16
Doppler	16 (36%)	83 (41%)	0.38
Male sex	37.0 (2.4)	36.6 (2.8)	0.37
Gestation at delivery (weeks)	-1.74 (0.47)	-1.82 (0.49)	0.31
z birthweight	-1.11 (0.75)	-1.39 (0.81)	0.04
z birth length	-0.79 (1.0)	-1.15 (0.81)	0.01
z birth HC			
Postnatal variables			
z weight 3 months	-0.91 (0.88)	-1.08 (0.85)	0.23
z length 3 months	-0.91 (1.1)	-1.21 (0.93)	0.05
z HC 3 months	-0.70 (1.1)	-0.82 (0.98)	0.06

Data are number (%) mean (SD) as appropriate

AC=abdominal circumference

HC=head circumference

8.3.2 Prediction Of Length

Mothers of short babies had a trend to different ethnic distribution compared to mothers of babies of normal length, with an over representation of European mothers in the short group (table 8.2). Significant perinatal associations with shortness at six months were: shortness at birth (z score birth length), male sex, birthweight, z birthweight, normal ponderal index , gestation at delivery and antenatal corticosteroids (table 8.2).

When these variables were entered into a logistic regression model only z score birth length [OR 2.6 (95% CI 1.6-4.4 for each standard deviation unit of birth length below the mean)], and male sex [OR 2.8 (95% CI 1.3-6.1 for male infants)] were found to be independent predictors of shortness at six months. In order to further investigate the factors which might be responsible for the over representation of male babies in those who were short at six months, z score birth length measurements (using sex adjusted centile charts) and ponderal indices at birth were compared by sex of the baby. There was no difference in z score length measurement at birth between boys [-1.50 (.97)] and girls [-1.46 (.86) $p=0.73$]. Thus the explanation for more boys being short at six months was not that they were shorter at birth.

Table 8.2 Maternal, fetal and newborn variables in relation to length at six months

Maternal variables	Length		P value
	Short n=40	Normal n=162	
Maternal age (years)	30 (4.8)	28.7 (6.0)	0.20
Height (cm)	160.0 (8.4)	162.3 (7.5)	0.14
Booking weight (kg)	63.1 (14.3)	62.4 (13.7)	0.80
Ethnic group			
European	36 (90%)	108 (67%)	0.05
Maori	2 (5%)	17 (10%)	
Pacific Island	1 (2.5%)	8 (5%)	
Other	1 (2.5%)	29 (18%)	
Parity			
0	21 (52%)	83 (51%)	0.26
1	15 (38%)	44 (27%)	
≥2	4 (10%)	35 (22%)	
Smokers	8/40 (20%)	48/159 (30%)	0.16
Pregnancy induced hypertension	17 (43%)	64 (40%)	0.81
Fetal and Newborn variables			
Gestation AC <10th% (weeks)	32.1 (26.4, 36.6)	33.6 (28.5, 36.9)	0.06
AC <10th% at <34 weeks	26 (65%)	91 (56%)	0.31
Abnormal UA Doppler	20 (50%)	67 (41%)	0.32
Antenatal corticosteroids	15 (38%)	32 (20%)	0.02
Gestation at delivery (weeks)	36.4 (31.1, 39.1)	37.3 (34.0, 39.5)	0.01
Birthweight (g)	1970 (788, 2512)	2247 (1430, 2701))	0.001
Male sex	26 (65%)	56 (35%)	0.0004
z score birthweight	-1.9 (-3.1, -1.4)	-1.7 (-2.4, -1.2)	0.02
z score birth length	-1.7 (-3.4-1.1)	-1.3 (-2.1, -0.4)	<0.0001
z score birth HC	-1.3 (-2.4, -0.1)	-1.2 (-2.2, -0.2)	0.44
Ponderal index >10th%	29 (73%)	79 (49%)	0.006

Data are mean (SD), median (10th,90th percentile) or number (%) as appropriate. HC=head circumference, AC=abdominal circumference, UA=umbilical artery

8.3.3 Prediction of weight

Mothers of underweight babies tended to be heavier at booking (67.1 versus 61.6 kg, $p=0.08$ table 8.3). In univariate analysis, low weight at six months was associated with: gestation at which the SGA was detected on antenatal scan, antenatal corticosteroid treatment, gestation at delivery, birthweight, z score birth head circumference and abnormal umbilical artery Doppler result. When these factors were entered into a logistic regression model, the only variable which had an independent effect on low weight at six months was the gestation of diagnosis of the SGA [OR 8.7 (95% CI 2.6-29.7) for those who were diagnosed SGA at 34 weeks]. No relationship was found between z birthweight and gestation at delivery ($R^2=0.002$, $p=0.48$).

Table 8.3 Maternal, fetal and newborn variables in relation to weight at six months

Maternal variables	Weight		P value
	Light n=31	Normal n=172	
Maternal age (years)	29.2 (5.8)	28.9 (5.8)	0.82
Height (cm)	163.5 (8.6)	161.5 (7.5)	0.28
Booking weight (kg)	67.1 (15.2)	61.6 (13.3)	0.08
Ethnic group			
European	25 (78%)	120 (70%)	0.59
Maori	3 (10%)	16 (9%)	
Pacific Island	2 (6%)	7 (4%)	
Other	2 (6%)	29 (17%)	
Parity			
0	17 (53%)	88 (51%)	0.23
1	12 (38%)	47 (27%)	
≥2	3 (9%)	36 (21%)	
Smokers	7 (23%)	50 (30%)	0.42
Pregnancy induced hypertension	15 (48%)	67 (40%)	0.38
Fetal and Newborn Variables			
Gestation AC <10th% (weeks)	30.8 (26, 34)	33.9 (28.7, 37.4)	<0.0001
AC <10th% at <34 weeks	28 (90%)	89 (52%)	<0.0001
Abnormal UA Doppler	17 (53%)	60 (35%)	0.03
Antenatal corticosteroids	16 (52%)	31 (18%)	<0.0001
Gestation at delivery (weeks)	35.4 (29.8, 38.9)	37.3 (34.1, 39.5)	0.0003
Birthweight (g)	1740 (703, 2529)	2245 (1451, 2708)	0.0003
Male sex	14 (44%)	69 (40%)	0.85
z score birthweight	-1.7 (-3.1, -1.4)	-1.7 (-2.4, -1.2)	0.55
z score birth length	-1.6 (-3.5,-0.4)	-1.4 (-2.2, -0.1)	0.08
z score birth HC	-1.4 (-2.7, -0.4)	-1.2 (-2.2,-0.1)	0.04
Ponderal index >10th%	21 (69%)	87 (51%)	0.07

Data are mean (SD), median (10th, 90th percentile) or number (%) as appropriate.

HC=head circumference, AC=abdominal circumference, UA=umbilical artery

8.3.4 Prediction Of Smallness

Twenty two babies (11%) were both short and underweight (overall small) and 12 of these 22 (55%) also had small heads. In univariate analysis smallness at six months was associated with birthweight, z score birth length, ponderal index >10th percentile, gestation at diagnosis of SGA, gestation at delivery, and antenatal corticosteroids (data not shown). After logistic regression, gestation at delivery [OR 5 (95% CI 1.3-20) for delivery <37 weeks] and z score birth length [OR 2.27 (95% CI 1.3-4.3) for each standard deviation unit of birth length below the mean] were independently associated with overall smallness. There was a trend for gestation at diagnosis of SGA to be associated with overall smallness [OR 7.3 (95% CI 0.97-50)] for diagnosis of SGA at <34 weeks].

8.3.5 Prediction Of Head Circumference

Thirty seven babies (18%) had a head circumference <10th percentile at six months corrected age. The factors which were associated with head circumference <10th percentile in univariate analysis were: z score birth head circumference and z score birth length (table 8.4). There was a trend for more boys than girls to have a low head circumference. After logistic regression z score birth head circumference was the only independent predictor of low head circumference at six months [OR 4.6 (95% CI 2.6-8.2) for each standard deviation unit of birth head circumference below the mean]. Diagnosis of SGA at <34 weeks occurred in 24 (65%) of those with small heads and 92 (56%) of those with normal sized heads (p=0.31).

Table 8.4 Maternal, fetal and newborn variables in relation to head circumference at six months

Maternal variables	Head Circumference		P value
	Small n=37	Normal n=165	
Maternal age (years)	28.7 (6.4)	29.1 (5.7)	0.70
Height (cm)	160.5 (9.0)	161.9 (7.3)	0.43
Booking weight (kg)	62.2 (14.8)	62.4 (13.5)	0.95
Ethnic group			
European	26 (70%)	117 (71%)	0.98
Maori	4 (11%)	15 (9%)	
Pacific Island	1 (3%)	8 (5%)	
Other	6 (16%)	26 (15%)	
Parity			
0	19 (51%)	85 (52%)	0.88
1	11 (30%)	47 (28%)	
≥2	7 (19%)	33 (20%)	
Smoker	10/36 (28%)	47/163 (29%)	0.29
Pregnancy induced hypertension	14 (38%)	66 (40%)	0.80
Fetal and Newborn Variables			
Gestation AC <10th% (weeks)	32.9 (26.7, 36.4)	33.6 (28.1, 37.3)	0.11
AC <10th% at <34 weeks	24 (65%)	92 (56%)	0.31
Abnormal UA Doppler	17 (46%)	66 (40%)	0.50
Antenatal corticosteroids	9 (24%)	38 (23%)	0.88
Gestation at delivery (weeks)	37.0 (32.0, 40.0)	37.3 (33.1, 39.4)	0.21
Birthweight (g)	2055 (913, 2592)	2230 (1280, 2700)	0.08
Male sex	20 (54%)	62 (38%)	0.06
z score birthweight	-1.8 (-2.8,-1.4)	-1.8 (-2.4,-1.3)	0.11
z score birth length	-1.8 (-3.2,-0.9)	-1.5 (-2.4,-0.4)	0.02
z score birth HC	-1.5 (-2.5,-1.0)	-1.0 (-1.9, -0.1)	<0.0001
Ponderal index >10th%	21 (57%)	86 (52%)	0.63

Data are mean (SD), median (10th,90th percentile) or number (%) as appropriate.

HC=head circumference, AC=abdominal circumference, UA=umbilical artery

8.3.6 Other Morphometry And Catchup Growth

The interrelationship of other morphometric measurements obtained at the six month assessment was also assessed. Sixty percent of short babies were also under weight and 39% had a low head circumference. A similar proportion of underweight babies were short (58%) and 60% had a low head circumference. Of babies with low head circumference measurements 14 (38%) were short and 18 (58%) were underweight.

Δz scores were calculated as an estimate of catchup growth in length, weight and head circumference with a negative Δz score implying failure of catchup growth.

Seventy eight percent (31/40) of babies who were short at six months had a negative Δz score compared with 15% (24/161) of those with normal length ($p < 0.0001$).

Seventy four percent (23/31) of underweight babies had a negative Δz score compared with 10/172 (6%) of those with normal weight ($p < 0.0001$). Seventy six percent (28/37) of babies with small heads at six months had a negative Δz score compared with 20% (34/165) of those with normal head size at six months ($p < 0.0001$). Thus approximately three quarters of babies who failed to catchup by six months, for each parameter, were actually growing at below average velocity over that period.

8.4 DISCUSSION

This is the first study to report on the influence of a range of perinatal variables on the outcomes length, weight, and head circumference at six months corrected age in a cohort of children who were SGA at birth. In our study the perinatal factors associated with shortness, underweight, and low head circumference at six months

of age were different. Shortness at six months was associated with shortness at birth and male sex, low head circumference with small birth head size, whereas low weight at six months was associated with early detection of SGA antenatally. Overall smallness (low weight and height) was associated with early gestation at delivery and z score birth length.

Only one other series has addressed the importance of the time of onset of SGA antenatally in relation to postnatal growth (Fancourt et al 1976). In that study, conducted in the early 1970s, SGA was diagnosed on the basis of a small head (biparietal diameter) on antenatal ultrasound. Children recognised as SGA before 34 weeks gestation were more likely to be underweight, short, and have a low head circumference at four years. In our study there was also a significant association between a diagnosis of SGA before 34 weeks and underweight at six months. Using this cut off detected 90% of children who were underweight at six months but the positive predictive value (24%) was too low for this to be a clinically useful test. In our study, time of diagnosis of SGA antenatally was the only independent predictor of low weight, but did not predict shortness, or small head circumference at six months. As head growth is maintained in the growth restricted fetus at the expense of growth of the body, it is likely that the children in Fancourt's series, all of whom had small ultrasound head measurements in utero, and were not delivered until term, had more severe growth restriction than those in the current series.

Shortness at six months of age in our study was independently associated with shortness at birth and with male sex. There are no previous reports of perinatal predictors of length at six months of age. Two previous studies of the prediction of

height at two years in SGA babies reported that birth length standard deviation score was an important predictor of height at two years (Hokken-Koelega et al 1995, Leger et al 1997). Neither of these reports commented on whether the sex of the child was associated with height at two years. Only one previous study has specifically addressed catch up growth in height in relation to sex of the child (Albertsson-Wikland et al 1993). In this longitudinal study boys born SGA had more rapid catchup growth in weight than girls. However at four years of age twice as many boys as girls remained short which is consistent with the results in the current study. Confirmation of this difference in length between boys and girls in our study will need to wait until the final analysis is completed when the whole cohort reach two years of age in 2000.

An effect of male sex was no longer found when overall smallness was considered. This was predicted by z score birth length and gestation at delivery. As no relationship was demonstrated, in this study, between gestation at delivery and z birthweight the effect of gestation on overall smallness is not explained by more growth restricted babies being delivered earlier. Poor postnatal growth is a recognised complication of very preterm delivery (Gillet et al 1986). In our study preterm delivery may have compounded the effects, on growth, of being born SGA.

In our study the only predictor of low head circumference at six months was small head size at birth. As the period of maximum velocity in postnatal head growth occurs in the first six months (Fitzhardinge & Inwood 1989, Leger et al 1997), it is possible that most babies with small heads at six months will not show further catch up in head growth when assessed at two years of age. Small head size in children

born SGA may be important as it has been associated with poor intellectual performance (Lipper et al 1981, Harvey et al 1982, Berg et al 1989).

Three quarters of the babies who were short, underweight, or had low head circumference at six months, also had slow growth postnatally as indicated by increasingly negative z scores between birth and six months of age. Thus these babies were not just those more severely affected at birth, but were truly those who were failing to show catch up growth after birth. These may be the subgroups of babies who have persisting poor growth later in childhood. Further followup of this cohort at two years of age will be necessary to confirm whether failure of catchup growth at six months is highly predictive of growth failure at two years.

Abnormal antenatal umbilical artery Doppler studies were not found to be independently associated with parameters of poor growth at six months. This is in keeping with the results of Marsal et al (1988) who found that abnormal antenatal aortic Doppler waveforms did not predict later growth in childhood. This is probably due to the fact that abnormal Doppler waveforms occur in pregnancies with earlier onset and more severe growth restriction and are not independent predictors of adverse outcome when birthweight and gestational age are controlled for (chapter 7). Similarly in this study normal birth ponderal index (another marker of more severe growth restriction) was not found to be independently associated with small size at six months, when other confounding factors were considered.

Although we were only able to measure at six months of age 82% of the babies initially enrolled in the study, it is unlikely that loss to follow-up substantially

influenced our findings. The babies lost to follow-up appeared as a group to be those less severely growth restricted at birth, and they had already shown considerable catch-up, particularly in head size, by three months of age. They were thus unlikely to contribute significantly to the group of babies whose failure to catch up was the main focus of this study, and their loss would tend to decrease rather than increase the differences we found between those who did and did not catch up by six months.

Continued poor growth postnatally is associated with later health problems. If it is possible to predict at the time of birth which babies will not experience catch up growth by six months it may be possible to offer treatment aimed at optimising subsequent growth. Currently there are no well established treatments. However there is one randomised, controlled trial of postnatal zinc supplementation of SGA newborn babies born in Chile (Castillo Duran et al 1995), in which zinc supplemented infants experienced better postnatal growth in both weight and length, at six months, than placebo treated infants. Further trials are necessary to confirm or refute this effect both in developing and developed countries. There is a single published randomised double blind trial of nutritional supplementation (nucleotide fortified formula) versus standard milk formula to improve postnatal growth in newborn term SGA babies (Cosgrove et al 1996). At six months of age nucleotide supplemented babies had improved growth in weight, length and head circumference compared with babies fed a standard milk formula. Further studies of nutritional supplementation are therefore warranted. Longer term followup to determine if initial growth benefits are maintained later in childhood, are also necessary.

CHAPTER 9

PERINATAL PREDICTORS OF NEURODEVELOPMENTAL OUTCOME IN SMALL FOR GESTATIONAL AGE CHILDREN AT 18 MONTHS OF AGE

9.1 INTRODUCTION

The findings from studies reporting neurodevelopmental outcome in children born SGA are inconsistent. The factors contributing to these apparently conflicting results are reviewed in chapter 1. A number of the studies have reported significant differences in a range of neurodevelopmental outcomes between cohorts of SGA and AGA children. Others have identified subgroups of SGA to be at particular risk of poor neurodevelopmental outcome. The conflicting study results are compounded by the fact that neurodevelopmental outcomes have also been reported to change as the SGA child matures with more abnormal test results, especially behavioural problems and learning difficulties, becoming manifest with increasing age (Low et al 1992). It is difficult to detect these learning difficulties and other minor neurological problems such as poor coordination and balance before school age (Fitzhardinge 1985).

The relationship between perinatal variables and neurodevelopment in SGA children has been examined in a number of studies and is reviewed in chapter 3 of this thesis. This information will therefore only be briefly summarised in this chapter.

Only one series has reported neurodevelopmental outcome in relation to time of onset of IUGR (Fancourt et al 1976, Harvey et al 1982). Small head size at <26 weeks gestation was associated with more abnormal neurodevelopmental outcomes at four (Fancourt et al 1976) and five years of age (Harvey et al 1982).

Three well designed studies have reported the relationship between the severity of growth restriction and later neurodevelopmental outcome. The results of these studies vary. A relationship has been reported between birthweight deviation and minor neurological dysfunction at seven years (Ley et al 1996¹) but not with IQ at a mean age of 28 months (Soothill et al 1995) or at six years (Ley et al 1996²).

There are a number of studies which have explored the influence of antenatal fetal Doppler studies on subsequent neurodevelopmental outcome in SGA babies (Ley et al 1996^{1&2}, Wilson et al 1992, Todd et al 1992, Valcamanico et al 1994, Scherjon et al 1993, Chan et al 1996) and these studies are reviewed in more detail in chapter 3. Two well designed studies (Ley et al 1996^{1&2}) found that abnormal aortic Doppler waveforms were associated with minor neurological dysfunction (Ley et al 1996¹) and lower global IQ at seven years (Ley et al 1996²). The two reports of antenatal cerebral Doppler studies and later neurodevelopment did not demonstrate a relationship between abnormal umbilical/cerebral Doppler resistance ratios and abnormal neurodevelopment at 12 months (Scherjon et al 1993) or two years (Chan et al 1996).

IUGR associated with a normal ponderal index has been termed symmetric or proportionate IUGR (Villar et al 1984). It has been hypothesised that proportionate

IUGR has its onset earlier in pregnancy than disproportionate or asymmetric IUGR which is characterised by a low ponderal index (Berg 1989). SGA children with symmetric IUGR have been reported to have worse neurodevelopmental outcomes (Villar et al 1984). In another study where SGA children were classified according to ponderal index, hypoxia related factors at birth, not ponderal index, were found to be related to neurologic morbidity at seven years (Berg 1989). Other investigators have also reported lower neurodevelopmental test scores in subgroups of SGA who were asphyxiated as neonates. (Fitzhardinge 1985, Tenovuo et al 1988). A linear relationship between pH in fetal blood obtained at cordocentesis and Griffiths Developmental quotient has also been reported (Soothill et al 1995).

In many of the studies of developmental outcome in SGA children in the first 2 years of life, the children were born in the 1960s and 70s (Harvey 1976, Low et al 1978, Commey & Fitzhardinge 1979, Villar et al 1984, Fitzhardinge 1985). Since that time a number of changes have occurred, in obstetric and especially in neonatal practice, which may have resulted in improved outcomes for SGA children born in the 1990s, compared with those born in previous decades.

The aims of the current study were to:

- 1) assess neurodevelopmental outcome at 18 months, using Bayley Scales of Infant Development II (BSID II), in a cohort of SGA children born in the mid 1990s
- 2) compare the results of the components of the BSID II from the SGA cohort with a reference population

3) identify whether one or more of the following perinatal variables were predictive of abnormal test results in the mental, motor, or behaviour rating scales of the BSID II:

- early recognition of SGA antenatally
- an abnormal umbilical artery Doppler result or abnormal umbilical/cerebral resistance ratio
- lack of participation in the antenatal studies of SGA pregnancies
- gestation at delivery
- head size at birth
- head growth from birth to six months
- ponderal index at birth

9.2 METHODS

9.2.1 General

SGA babies born between 1993 and 1997 were recruited to the postnatal study of neurodevelopment which is still ongoing (see General Methods, chapter 4).

Neurodevelopment is assessed at 18, 36 and 72 months corrected age. This chapter reports on the results, to date, of developmental assessment at 18 months corrected age using the BSID II. The BSID was developed by cataloguing normal child development and enables the comparison of individual performance with that of age matched groups from a general North American population (Bayley 1993). It was developed to identify areas of relative impairment or delay and to introduce interventions which could then be tested to see if they improved performance. The test can be applied from one to 42 months corrected age and the components are modified according to the age of the child.

The BSID II was chosen as the assessment instrument in this study as it has been updated in 1993 to include items which may be more predictive of later performance in intelligence quotient tests and because it is a widely used instrument which enables comparison with other studies. The BSID II consists of three separate areas of testing. The mental developmental index (MDI) assesses the child's current level of cognitive, language, personal and social skills development. The motor developmental index (PDI) assesses the control of gross and fine muscle groups. The behaviour rating scale (BRS) assesses the child's behaviour during the testing situation and reflects adaptation to the environment. The three scales are complementary and normal ranges for each of the scores have been well established in a representative sample of the North American population (Bayley 1993). The MDI and PDI scales are set so that the mean score is 100 and standard deviation is 15. Mild developmental delay is defined as a score between 70 and 84 and a score of ≤ 69 is defined as significant developmental delay (Bayley 1993). For the BRS the median value in the general population (aged between 13 and 42 months, $n=900$) is 109.2 and the tenth percentile is 93. An abnormal (non optimal result) is <93 (Bayley 1993).

The MDI and PDI scores were classified as abnormal for the purposes of this study if the result was <1 SD below the mean for the general population (<85). The behavioural rating score was classified as abnormal if the result was less than the tenth percentile (<93) for the general population (Bayley 1993).

The developmental assessment was performed by a psychologist trained in the use of the BSID II in a research clinic room containing the necessary equipment and

standardised assessment conditions. The developmental scores were adjusted if necessary (as outlined in the Bayley manual) to the corrected postnatal age of the child.

A measurement of growth rate (Δ z score) from birth to six months was calculated for head circumference, length and weight as the difference between z score measurement at six months and birth. A negative result was defined as abnormal implying failure of catchup growth between birth and six months.

9.2.2 Statistical Methods

Statistical analysis was carried out using Statview (SAS Institute, 2nd edition 1998). Values are expressed as mean (SD), for normally distributed data and median (10th, 90th percentiles) when data were not normally distributed. Relationships between continuous variables were assessed using linear regression for normally distributed data, or Spearman Rank correlation when data were not normally distributed. Logistic regression was used to determine which of the variables identified in univariate analysis were independently associated with low MDI, PDI or BRS scores. Multivariate analysis was used to determine which of the variables found to have a significant effect in univariate analysis were independently associated with total MDI, PDI and BRS. A logarithmic transformation was performed for newborn hospital and nursery days, before they were used in multivariate analysis.

9.3 RESULTS

9.3.1 General

Of the 248 SGA babies who have been recruited to the study 148 had completed the 18 month neurodevelopmental assessment at the time that this analysis was performed (December 1998). A full report will be presented when the whole cohort has completed assessment at 18 months in the year 2000 and subsequently when the cohort has completed developmental assessment at 36 and 72 months. One hundred and forty seven children completed full testing (MDI, PDI, and BRS) and one child completed MDI and BRS but did not complete the PDI because he became distressed. Seventy one (48%) of the children had participated in one of the two antenatal studies in SGA pregnancies reported in this thesis (chapters 5 and 6) in which fetal wellbeing was monitored at regular intervals by a research midwife.

The mean MDI result in our cohort of SGA babies was significantly different to that in the reference sample [95.8 (14.3) versus 100 (15) respectively, $p=0.03$] (Bayley 1993). Twenty seven children had abnormal MDI results 20 (13%) with mild developmental delay and seven (5%) with severe developmental delay. The corresponding rates in the reference sample for mild developmental delay was 13 (13%) and for severe developmental delay was 2 (2%), $p=0.27$. Twenty two children had abnormal PDI results. Sixteen (11%) had mild developmental delay which was not different to the rate in the reference sample [12 (12%)]. The prevalence of significant developmental delay also did not differ between SGA 6 (4%) and the reference sample 2 (2%), $p=0.27$.

Median BRS results did not differ between our cohort of SGA (109.6) and the reference sample (109.2). However more children in our cohort had scores <10th percentile [23 (16%) compared with 90/900 (10%) in the general population, $p=0.04$].

Significant correlations were found between the three test scores (MDI and PDI, $R^2=0.31$ $P<0.0001$, MDI and BRS, $R^2=0.20$ $P<0.0001$ and PDI and BRS $R^2=0.12$, $P<0.0001$).

Of the 27 children with abnormal MDI results 11 (41%) had low PDI scores and nine (33%) had low BRS results. Of the 22 children with abnormal PDI scores 11 (50%) had low MDI scores and seven (32%) had low BRS results. Nine (39%) of the 23 children with low BRS results had abnormal MDI scores and seven (30%) had low PDI scores. Only three children had abnormal results for all three components of the BSID II test.

9.3.2 Bayley Test Results In Relation To Parental Characteristics

In univariate analysis, caesarean section for fetal distress was less common in the mothers of children who had a low MDI score compared to those with normal scores (table 9.1). They also had a trend to less pregnancy induced hypertension [6 (22%) versus 52 (44%) $p=0.05$] compared to mothers of children with normal MDI scores. Mothers of children with an abnormal BRS were younger than those with a normal score [27.5 (5.7) versus 30.0 (5.2) respectively, $p=0.04$] but no maternal variables were found to be predictive of a low PDI score. Maternal educational status was known in 84/148 (57%) and educational level was not related to abnormal neurodevelopmental testing at 18 months.

Table 9.1: Pregnancy characteristics in relation to neurodevelopmental assessment at 18 months

Parental characteristics	MDI		PDI		BRS	
	Abnormal <85 n=27	Normal ≥85 n=121	Abnormal <85 n=22	Normal ≥85 n=125	Abnormal <93 n=23	Normal ≥93 n=125
Maternal						
age (yrs)	29.1 (6.3)	29.7 (5.1)	29.0 (6.1)	29.7 (5.2)	27.5 (5.7)	30.0 (5.2)*
education						
<3 yrs sec	3 (20%)	16 (23%)	3 (27%)	16 (22%)	1 (10%)	18 (24%)
4-6 yrs sec	2 (13%)	19 (28%)	3 (27%)	18 (25%)	3 (30%)	18 (24%)
tertiary	10 (67%)	34 (49%)	5 (46%)	38 (53%)	6 (60%)	38 (52%)
Smokers	8/26 (31%)	38/119 (32%)	8/21 (38%)	38/123 (31%)	6/23 (26%)	40/122 (33%)
PIH	6 (22%)	52 (44%)	8 (36%)	49 (39%)	6 (26%)	52 (42%)
Total LSCS	8 (30%)	49 (40%)	9 (41%)	48 (38%)	9 (39%)	48 (38%)
LSCS fetal distress	2 (7%)	30 (25%)*	5 (23%)	26 (21%)	4 (17%)	28 (22%)
Paternal						
employment	14/17 (82%)	61/69 (88%)	12/14 (80%)	62/71 (87%)	11/13 (85%)	64/73 (88%)

Values are mean (SD), * P<0.05,

sec=secondary, PIH=pregnancy induced hypertension

9.3.3 Bayley Test Results In Relation To Fetal And Newborn Characteristics

A low ponderal index at birth and not participating in one of the antenatal SGA studies were associated with a low MDI score in univariate analysis (table 9.2). These variables, and also the maternal variables associated with a low MDI score, (caesarean section for fetal distress, and pregnancy induced hypertension) were entered into a logistic regression model to determine which factors were independently associated with a low MDI score. After logistic regression, only low ponderal index, OR 2.6 (95% CI 1.1-6.4), and non participation in the antenatal SGA studies, OR 2.7 (95% CI 1.1-6.6) were independently associated with a low MDI score. Maternal age and z score birth head circumference were entered into a

logistic regression model to determine which factors were independently associated with a low BRS . Low BRS was significantly associated with low z score head circumference at birth, OR 2.8 95% CI (1.5-5.2) for each standard deviation unit of birth head circumference below the mean (table 9.2). None of the fetal and newborn variables investigated were associated with a low PDI score.

Overall girls had slightly higher scores than boys for the three assessments 96.8 (14.6) versus 94.4 (13.7) for MDI, 97.4 (13.9) versus 96.5 (15.4) for PDI and 108.1 (13.9) versus 105.8 (11.1) for the BRS but no differences were statistically significant.

Cord arterial pH results were available at birth in 90/148 (61%) with mean (SD) of 7.29 (0.08). Only three babies had values <7.15 (7.12, 7.12, 7.13). One baby had a low five minute apgar score (<6) and no babies had hypoxic ischaemic encephalopathy or newborn seizures. There were no differences in mean pH results between those with normal or abnormal MDI, PDI or BRS scores (data not shown).

Table 9.2: Fetal and newborn variables in relation to neurodevelopmental assessment at 18 months

	MDI		PDI		BRS	
	Abnormal <85 n=27	Normal ≥85 n=121	Abnormal <85 n=22	Normal ≥85 n=125	Abnormal <93 n=23	Normal ≥93 n=125
Fetal variables						
Gestation AC	32.9 (3.4)	33.0 (3.2)	32.4 (3.6)	33.1 (3.2)	32.8 (3.5)	33.0 (3.3)
<10th% (weeks)						
Antenatal SGA	8 (30%)	63 (52%)*	9 (41%)	61 (49%)	10 (43%)	61 (49%)
study						
Abnormal UA	12 (44%)	47 (39%)	11 (50%)	47 (38%)	6 (26%)	53 (42%)
Doppler						
Abnormal	6/12 (50%)	38/68 (56%)	7/11 (64%)	37/68 (54%)	8/11 (73%)	36/69 (52%)
CA/UA ratio						
Corticosteroids	4 (15%)	29 (24%)	6 (27%)	27 (22%)	5 (22%)	28 (22%)
TRH	1 (4%)	10 (8%)	3 (14%)	8 (6%)	2 (9%)	9 (7%)
Newborn variables						
Male sex	13 (48%)	43 (35%)	9 (41%)	47 (37%)	8 (35%)	48 (38%)
Gestation at	37.3 (2.5)	36.5 (2.7)	35.8 (3.0)	36.8 (2.6)	36.9 (3.1)	36.6 (2.6)
delivery (weeks)						
Z score weight	-1.9(-2.6,-1.4)	-1.7(-2.3,-1.2)	-1.7(-2.6,-1.4)	-1.7(-2.3,-1.2)	-1.8(-2.3,-1.3)	-1.7(-2.4,-1.2)
Z score length	-1.2(-2.3,-0.2)	-1.3(-2.1,-0.5)	-0.9(-2.7,-0.1)	-1.4(-2.1,-0.5)	-1.3(-1.9,-0.6)	-1.4(-2.2,-0.3)
Z score HC	-1.2(-2.5,-0.1)	-1.0(-2.0,0.0)	-1.1(-2.2,0.2)	-1.0(-2.0,-0.2)	-1.5(-2.8,-0.8)	-0.9(-1.9,0.0)**
Ponderal index	9 (33%)	68 (56%)*	9 (41%)	68 (54%)	10 (43%)	67 (54%)
>10th%						
Hypoglycemia	11/23 (48%)	52/114 (46%)	13/21 (62%)	50/115 (43%)	11/21 (52%)	52/116 (45%)

Values are mean (SD), number (%), median (10th, 90th percentile) as appropriate;

* p <0.05; ** p <0.001;

CA/UA ratio =cerebral umbilical artery Doppler resistance ratio, UA=umbilical artery,

AC=abdominal circumference, HC=head circumference, TRH=thyrotropin releasing hormone

9.3.4 Bayley test results in relation to postnatal growth

Data from assessment of growth and size at six months were available in 131/148 (89%) of cases. No relationship was found between a range of measures of body size and growth at six months and low MDI, PDI or BRS (table 9.3). There was a trend to an association between overall smallness (weight and length <10th%) and low PDI and BRS scores. Those who were overall small accounted for 25% (5) of those with low PDI and BRS scores compared with 10% (11) of those with normal PDI and BRS scores ($p=0.06$).

Table 9.3: Postnatal growth parameters at six months in relation to neuro-developmental assessment

6 mth growth parameters n=131	MDI		PDI		BRS	
	Abnormal <85 n=23	Normal ≥85 n=108	Abnormal <85 n=20	Normal ≥85 n=110	Abnormal <93 n=20	Normal ≥93 n=111
HC <10th%	2 (9%)	15 (14%)	2 (10%)	15 (14%)	4 (20%)	13 (12%)
Length <10th%	5 (22%)	21 (20%)	7 (35%)	19 (17%)	6 (30%)	20 (18%)
Weight <10th%	5 (22%)	17 (16%)	5 (20%)	15 (14%)	6 (30%)	16 (14%)
Weight + length <10th%	5 (22%)	11 (10%)	5 (25%)	11 (10%)	5 (25%)	11 (10%)
Abnormal head growth	6 (26%)	31 (29%)	6 (30%)	31 (28%)	5 (25%)	32 (29%)
Abnormal length growth	4 (17%)	34 (32%)	7 (35%)	31 (28%)	7 (35%)	31 (28%)
Abnormal weight growth	4 (17%)	19 (18%)	5 (25%)	18 (16%)	4 (20%)	19 (15%)

Values are number (%), median (10th, 90th percentile) as appropriate. HC=head circumference

The relationships between a number of perinatal and postnatal continuous variables and total MDI, PDI and BRS results were assessed by linear regression and the correlation coefficients were calculated (table 9.4).

Table 9.4: Correlation coefficients between continuous perinatal and postnatal variables and neurodevelopment test scores

	MDI score		PDI score		BRS	
	R ²	P value	R ²	P value	R ²	P value
Perinatal	0.005	0.42	0.02	0.12	0.002	0.57
Gestation AC <10th%						
Last umbilical artery Doppler resistance index	0.01	0.24	0.025	0.06	0.001	0.65
Gestation at delivery	<0.001	0.99	0.05	0.009	0.001	0.67
Cord arterial pH	0.005	0.50	0.04	0.06	0.005	0.50
Newborn nursery days*	-0.08	0.34	-0.25	0.002	-0.17	0.04
Newborn hospital days*	-0.04	0.64	-0.23	0.005	-0.18	0.03
z birth HC	0.007	0.29	<0.001	0.79	0.07	0.001
z birth weight	0.019	0.09	<0.001	0.83	0.02	0.06
z birth length	0.003	0.52	<0.001	0.85	<0.001	0.67
Birth ponderal index	<0.001	0.85	0.03	0.03	0.017	0.12
Postnatal						
z HC 6 months	0.001	0.78	0.008	0.31	0.03	0.04
z weight 6 months	0.004	0.49	0.022	0.09	0.03	0.03
z length 6 months	0.001	0.78	0.009	0.28	0.001	0.73
Head growth	0.001	0.78	0.001	0.74	<0.001	0.87
Weight growth	<0.001	0.86	0.025	0.04	0.016	0.15
Length growth	0.003	0.51	0.01	0.22	<0.001	0.99

*Spearman rank correlation with RHO corrected for ties instead of R²;

bold figures indicate statistically significant results;

HC=head circumference

The MDI score was not found to be correlated with any of the variables which were tested. The PDI score was correlated negatively with newborn nursery and newborn

hospital days, and positively correlated with gestation at delivery, ponderal index, and weight growth. However, after multivariate analysis the only variable which was independently associated with PDI score was log newborn nursery days with a seven point reduction in PDI score for each log unit of nursery stay (e.g a seven point reduction in PDI score for a change from a one day to a 10 day nursery stay). After multivariate analysis the BRS was found to be independently related to z birth head circumference with a five point reduction in BRS for each z score unit of head circumference below the mean.

9.4 DISCUSSION

The 18 month old SGA children in this study of neurodevelopmental outcome were found to have mean PDI and median BRS results similar to those found in a North American reference sample (Bayley 1993). The mean MDI result differed significantly from the mean in the reference sample (95.8 versus 100). No difference was detected in rates of 'mild' or 'significant' developmental delay on MDI or PDI scales compared to the reference sample but a larger study group (n=650) is required to determine whether a difference exists in the rate of 'significant' developmental delay. More SGA children were found to have low behavioural rating scores 23 (16%) than children in the reference sample 90 (10%) $p=0.04$. The above results need to be interpreted with some caution due to the lack of a local control group, however they are consistent with the results of a New Zealand study of SGA children born in the early 1990s where significant differences were found in behavioural rating (but not MDI or PDI) scores between SGA and AGA controls (Pryor 1996).

Three series have compared neurodevelopmental results, in the first two years of life, between SGA and AGA children born in the 1960s to early 1980s. These studies reported significantly lower scores on all three components of the Bayley Scale in SGA children (Low et al 1978), lower total cognitive scores in SGA than in AGA controls (Villar et al 1984), and more abnormal results on Denver Developmental screening (Tenovuo et al 1988). In the study by Tenovuo et al (1988) the main risk factor for abnormal neurodevelopmental outcome at two years in SGA children was asphyxial complications in the perinatal period. The relationship between abnormal neurodevelopment and asphyxia was also reported in a series of low birthweight (<2500 gm) infants, 43% of whom were SGA (Spinillo et al 1995). The rate of possible asphyxial complications in our cohort was low (three cases of mild acidosis at birth, one case of low five minute apgar, no hypoxic ischaemic encephalopathy) and along with improvements in neonatal care may be one factor contributing to the better overall neurodevelopmental results in our study compared to reports from some earlier series.

Low behavioural rating scores are a reflection of emotional lability and poor task orientation. The finding of more low scores in this study of SGA children at 18 months of age is interesting as studies of SGA children at nine to eleven years have shown a high prevalence of behaviour problems, inattention and learning difficulties (Low et al 1992). Similarly adolescent SGA subjects have been reported to have a higher rate of behaviour problems than AGA controls (Pryor et al 1995). Long term followup of this current cohort to school age will confirm whether abnormalities in the BRS at 18 months are predictive of later learning and behaviour problems. If these

behavioural differences can be detected in infancy then early interventions, which may improve later performance (Watt 1990), would warrant further evaluation.

In this study different perinatal factors were found to be predictive of low scores in the three components of the BSID II test. After logistic regression two independent risk factors were identified for a low MDI score, not being involved in the antenatal studies of SGA pregnancy and a low ponderal index at birth. Those who participated in the antenatal studies received regular tests of fetal surveillance, regular growth scans, and regular clinical checks by the same research midwife. This vigilant antenatal care may have resulted in some long term benefits to the participants in these studies. The results of previous studies which have examined the relationship between birth ponderal index and neurodevelopment are conflicting. Villar et al (1984) reported that a normal ponderal index in Guatemalan babies, was associated with lower neurodevelopmental scores at two years. Another study in SGA children reported that hypoxia at birth was predictive of abnormal neurological development not ponderal index grouping (Berg et al 1989). Further follow up of the remaining children in our SGA cohort will help to determine if the association found in this study between low ponderal index and low MDI score is real, as it has not been previously reported.

The current study is the first to report a relationship between small birth head size and low BRS. Postnatal head growth was not associated with BRS which suggests that the brain development which is important for this component of the BSID II occurs predominantly in fetal life. Previous studies have also found that small head size in fetal life (Harvey et al 1982) and at birth (Lipper et al 1981) were associated

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with abnormal neurodevelopmental testing. Another report (Berg et al 1989) of neurological examination in seven year old SGA children, found that low birth head circumference as well as hypoxia, was predictive of abnormal neurological examination. A recent follow up study (n=2719 SGA infants) found that SGA infants with birth head circumference <31 cm had the lowest IQ scores at seven years of age (Strauss et al 1998). If the relationship between birth head size and BRS, found in this study, is confirmed when the whole cohort has completed followup to 18 months, and if low BRS is found to be predictive of later learning problems, then early intervention in SGA children with low head circumference may warrant evaluation.

Total PDI score was found to be inversely correlated with the log of newborn nursery days which is a reflection of gestation at delivery. Abnormal motor developmental testing at 18 months may be related to motor problems later in childhood, including cerebral palsy (unpublished observations, Dezoete 1998). The most important risk factor for cerebral palsy is preterm birth (Escobar et al 1991) and SGA is an additional risk factor (Blair & Stanley 1990). Long term follow up of the cohort in this study is ongoing and will determine the prevalence of later motor problems including cerebral palsy and whether there is an association with abnormal PDI scores at 18 months.

In this study abnormal umbilical artery Doppler studies did not predict abnormal neurodevelopmental scores and the last umbilical artery Doppler resistance index before delivery was not correlated with total MDI, PDI or BRS. Two studies which found an association between abnormal aortic Doppler waveforms and later minor neurological dysfunction (Ley et al 1996¹) and total IQ (Ley et al 1996²) performed

their assessments on school age children. Our cohort will also be followed up until six years of age at which time the relationship between umbilical artery Doppler studies and neurodevelopment will be further assessed. In our study as in others (Scherjon et al 1993, Chan et al 1996), an abnormal cerebral / umbilical resistance ratio was not correlated with abnormal neurodevelopmental testing at 18 months.

Being born SGA is only one factor of the many which may contribute to neurodevelopmental variability in children. Other important factors include maternal intelligence and education, socioeconomic status, home environment, and attendance at preschool (Goldenberg et al 1998). At least some of the factors associated with a baby being born SGA (e.g socioeconomic status) may affect later neurodevelopmental outcome independent of an effect on birth size. In this study, low maternal educational level, a marker of socioeconomic status (Bradley et al 1989), was not associated with low developmental scores. Previous studies have found correlations between maternal education and IQ in two and six year old children (Cohen & Parmelee 1983; Bradley & Caldwell 1989). Consistent associations have not been found between maternal education and developmental assessment in 12 month old children (Slater 1995). There are a number of possible explanations for the lack of association between Bayley scores at 18 months and maternal education found in this study. Environmental factors such as maternal education may influence child development in the post infancy period (Slater 1995) and/or Bayley tests at <2 years may not be predictive of later IQ (Slater 1995). An alternative explanation is that due to the incomplete data on maternal education in this study, (57%), an effect of maternal educational status may have been missed.

We are now attempting to collect the missing data and will comment further on maternal education and Bayley scores when the full cohort reaches 18 months.

9.5 SUMMARY

The 18 month old SGA children in this cohort were found to have more low BRS scores and lower mean MDI results than the reference sample. Not participating in our antenatal SGA research projects and low ponderal index at birth were independently predictive of a low MDI score. The PDI score was negatively correlated with newborn nursery days and BRS results were correlated with head size at birth. The overall outcomes however were generally good and may be related to a low rate of asphyxia and to improvements in obstetric and neonatal care in the 1990s. The results obtained in this interim report will require confirmation when the whole SGA cohort reaches 18 months of age. Assessment of the same cohort at 36 and 72 months will provide valuable additional information as to whether neurodevelopmental assessment changes with time in SGA children.

CHAPTER 10

FUTURE DIRECTIONS AND CONCLUSIONS

Being born small for gestational age can be associated with a range of complications which span the duration of the human life cycle.

Study 1 The first study presented in this thesis was a randomised controlled trial of a therapeutic intervention (aspirin 100mg) in SGA pregnancies with a placental vascular lesion, reflected by abnormal umbilical artery Doppler studies. In this study no therapeutic effect of aspirin on birthweight or other parameters of newborn size could be demonstrated. These results are consistent with those from a similar Western Australian study and are also in keeping with the results of the CLASP study. It can now be concluded that aspirin does not have a therapeutic role in the treatment of established fetal growth restriction. There are at least two possible explanations for the lack of a therapeutic effect from aspirin treatment. Data published after our study was commenced have suggested that disturbed prostanoid metabolism and platelet activation represent only a small part of the complex pathogenesis of fetal growth restriction. Alternatively it may be that treatment at the time that growth restriction is first recognised is too late in the pathophysiologic process to be of therapeutic benefit. Research into the underlying pathophysiology of fetal growth restriction is ongoing and is necessary to determine whether other therapeutic interventions warrant consideration in future trials of treatment of fetal growth restriction. If an effective therapeutic agent can be identified long term followup studies will be necessary to determine whether treatment aimed at

increasing birthweight can reduce the long term complications which are associated with being born SGA.

Although low dose aspirin does not have a role in the treatment of established growth restriction, prophylactic treatment of pregnant women at high risk of growth restriction, from early in pregnancy, with 100 or 150 mg of aspirin, significantly reduces the risk of an SGA baby. Further research effort is necessary to better identify these high risk pregnancies so that aspirin and/or other future prophylactic treatments can be administered to the pregnant women who will most benefit from them. Prophylactic treatment is particularly important as treatment initiated at the time that growth restriction is recognised may be too late.

Clinical risk scoring for fetal growth restriction in early pregnancy is of limited value in nulliparous women as one of the most important predictors is a previous growth restricted baby. Future research efforts to identify women at high risk of IUGR should consider combining clinical risk scoring with one or more biochemical markers. The role of raised maternal serum IGFBP-I in the second trimester warrants further evaluation as a screening test for fetal growth restriction.

Study 2: A pilot randomised controlled trial of two regimens of fetal surveillance in SGA pregnancies with normal umbilical artery Doppler studies was the topic of the second study presented in this thesis. Traditional practice in our institution and in others has been to monitor fetal wellbeing frequently when the fetus has been recognised to be SGA before birth. This practice increases costs of healthcare as well as anxiety for the women, and benefit to the pregnancy had not previously been

evaluated. In this study planned twice weekly pregnancy surveillance was associated with less spontaneous onset of labour due to an increase in induction of labour. Women who underwent planned twice weekly surveillance were delivered four days earlier and had a trend to fewer SGA babies. This study had sufficient power to detect a difference in the rate of spontaneous labour between study groups but not to detect differences in serious newborn or maternal morbidity. To determine whether less frequent surveillance is safe would require a trial with at least 2000 participants. A trial of this magnitude would need to be multicentred and appropriately funded. The feasibility of conducting such a trial will now be explored by discussions with other large perinatal centres in Australia and New Zealand. However, a number of centres in Australia and New Zealand already have guidelines for surveillance in SGA pregnancies which are based on umbilical artery Doppler studies. It is therefore possible that such a trial would not be a high research priority in these centres. If a multicentre trial is not feasible the data obtained from this pilot study will be used to develop guidelines for care in SGA pregnancies with normal umbilical artery Doppler studies at National Women's Hospital. In this study of SGA pregnancies with normal umbilical artery Doppler studies only 1/167 (0.6%) developed signs of fetal distress prior to the onset of labour. The risk of antenatal fetal compromise is therefore very low and fetal surveillance can probably safely be carried out less frequently than twice weekly. A further research question in this low risk group of SGA pregnancies which needs to be addressed is whether any antenatal tests of fetal wellbeing are necessary.

Study 3: This is the first study to report perinatal outcome in SGA babies in relation to umbilical artery Doppler status, taking into consideration the confounding

effects of both preterm delivery and birthweight. After logistic regression analysis umbilical artery Doppler status was not independently associated with newborn morbidity. Abnormal umbilical artery Doppler studies were associated with earlier onset and more severe growth restriction as well as earlier delivery implying a more severe disease process when compared to SGA babies with normal umbilical artery Doppler studies.

Although SGA babies with normal umbilical artery Doppler studies had low rates of serious perinatal complications, minor morbidity was common. One third were admitted to the newborn nursery and one quarter were hypoglycemic after birth. It can therefore be concluded that SGA babies with normal umbilical artery Doppler studies are not just 'small normal' babies and that careful monitoring, especially for hypoglycemia, is required in the newborn period.

Study 4: Previous studies in SGA babies have shown that most catch up growth in weight occurs in the first six months of life, and that most who are short at six months remain short at two years of age. Persisting short stature may be important because it has been associated with adverse psychological effects, under achievement at school and an increased risk of hypertension in childhood and adult life. This thesis contains the first report of perinatal predictors of size and growth at six months corrected age in SGA babies. In this study different factors were associated with shortness (shortness at birth and male sex), under weight (early detection of SGA antenatally) and small head circumference at six months (small birth head size). Further longitudinal study of this SGA cohort is necessary to determine the proportion of children who were small at six months who remain small

at two years of age. If, as expected, there are strong correlations between size at the two time periods (six and 24 months) then studies aimed at improving growth in those with perinatal risk factors will be justified.

The physiology and pathophysiology of postnatal human growth is still not fully understood and currently there are no well established therapeutic interventions. There is one randomised controlled double blind trial of postnatal zinc treatment of SGA babies, conducted in Chile. Zinc supplemented babies had better postnatal growth in weight and length at six months than placebo treated. Further trials of this apparently benign treatment are therefore required. Surprisingly there is only one report of a randomised controlled trial of a nutritional intervention to increase growth in SGA babies. In this study, non breast fed term SGA babies, received formula supplemented with nucleotides or ordinary formula. All parameters of growth at six months were improved in the nucleotide supplemented group. Further studies of nutritional interventions are necessary with longer term followup into childhood and beyond and may be considered by our research team. A suitable study group for future nutritional interventions may be the subgroups of SGA babies identified in this thesis who have perinatal risk factors for small size at six months.

Study 5: This is one of the first reports of neurodevelopmental outcome at 18 months corrected age in a cohort of SGA children born in the 1990s. A number of perinatal factors were identified which were associated with low scores in components of the Bayley scales. Of particular interest was the fact that the SGA cohort was found to have more low scores on the behavioural rating scale than the reference population. Low behaviour rating scores, which reflect emotional lability and poor task orientation, were associated with small head size at birth. Older SGA

children and adolescents have been reported to have a higher prevalence of learning difficulties and behaviour problems than AGA controls. This finding of more low behaviour rating scores in SGA children, which has been reported in one previous study, requires confirmation when the whole cohort (n=248) reaches 18 months of age. If it is confirmed, then longterm followup of our SGA cohort, to 72 months of age, will determine whether there is an association between abnormal behavioural rating scores at 18 months and later learning and behaviour problems. If such a relationship is confirmed, intervention early in childhood needs to be evaluated to determine whether later learning difficulties can be averted.

Not taking part in one of our antenatal studies in SGA pregnancies was independently associated with a low mental developmental index. Followup of the whole cohort to 18 months and beyond is necessary to confirm this association. Women who took part in the antenatal studies had regular pregnancy assessments with a dedicated midwife. If a benefit from this type of care is confirmed, the feasibility of introducing such a service as part of routine clinical practice for women with SGA pregnancies at National Women's Hospital will be investigated.

Women who took part in the antenatal studies described in this thesis consented to have samples of plasma stored at the time of recruitment and for newborn cord blood samples to be obtained at the time of delivery. A collaborative project is planned with Professors P Gluckman and J Harding, and Dr B Breier (Research Centre for Developmental Medicine and Biology, University of Auckland) to investigate whether maternal and / or fetal markers (especially IGFs and their binding proteins) might be

predictive of perinatal outcome and / or postnatal growth in SGA pregnancies.

Details of this planned project will be finalised over the next few months.

There is considerable overlap in the known pathophysiology of idiopathic fetal growth restriction and preeclampsia. Further studies are necessary to determine whether the two conditions represent different endpoints in the same disease process. Our team at National Women's Hospital has convened a meeting with co-investigators in Australia and the USA to discuss conducting a large screening study, utilising clinical and biochemical markers in the first half of pregnancy, to predict later preeclampsia and growth restriction. If funding applications are successful, knowledge gained from this study will also contribute to the understanding of the pathophysiology of these conditions.

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