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

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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
TGFα	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 ≤95th 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 Δ z 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.