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Effects of frequent ultrasound during pregnancy: a randomised controlled trial

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Summary

Despite widespread application of ultrasound imaging and Doppler blood flow studies, the effects of their frequent and repeated use in pregnancy have not been evaluated in controlled trials. From 2834 women with single pregnancies at 16–20 weeks gestation, 1415 were selected at random to receive ultrasound imaging and continuous-wave Doppler flow studies at 18, 24, 28, 34, and 38 weeks gestation (the intensive group) and 1419 to receive single ultrasound imaging at 18 weeks (the regular group). Outcome data was obtained from 99% of women who entered the study. The only difference between the two groups was significantly higher intrauterine growth restriction in the intensive group, when expressed both as birthweight <10th centile (relative risk 1·35; 95% confidence interval 1·09 to 1·67; p=0·006) and birthweight <3rd centile (relative risk 1·65; 95% confidence intervals 1·09 to 2·49; p=0·020). While it is possible that this finding was a chance effect, it is also plausible that frequent exposure to ultrasound may have influenced fetal growth. Repeated prenatal ultrasound imaging and Doppler flow examinations should be restricted to those women to whom the information is likely to be of clinical benefit.

Lancet 1993; **342:** 887–91

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Introduction

Ultrasound is widely accepted in clinical practice, and can improve the outcome of pregnancy. In a recently-reported randomised controlled trial, routine ultrasound screening at 16–20 weeks was shown significantly to reduce perinatal mortality, mainly due to early detection of fetal malformations.[1] Other studies have also shown the ability of ultrasound to estimate the age of the fetus,[2,3] improve the detection rate of intrauterine growth restriction (IUGR),[4-6] and reduce the incidence of induction of labour for post-term pregnancy.[5,7,8] Doppler ultrasound technology provides information on placental blood flow,[9] and systolic/diastolic ratios from flow velocity waveforms give an indirect assessment of placental vascular resistance. When used as primary screening tests in low-risk populations Doppler waveform studies have unacceptably high false-positive rates,[10] but when combined with other clinical and biometric information can assist in discriminating between those fetuses which are small because of normal genetic factors and those which are small because of intrauterine pathology.[11]

Despite widespread acceptance of these tests, there have been few attempts to measure the effects of frequent ultrasound examinations. The purpose of our study was to test the hypothesis that intensive use of ultrasound imaging and Doppler flow studies would improve pregnancy outcome expressed as days of neonatal stay and the rate of preterm birth. Those allocated to the intensive group of the trial would be compared with a similar number allocated to have a single ultrasound imaging study at 18 weeks, our current standard of practice. It was envisaged the intervention might improve pregnancy outcome by increasing the detection of fetal growth restriction and other disorders with resulting improvement in obstetric care.

Subjects and methods

Enrolment

Pregnant women attending the public antenatal clinic at King Edward Memorial Hospital, or nearby private practices between May 1989 and November 1991 were enrolled. The criteria for enrolment were gestational age between 16 and 20 weeks, sufficient proficiency in English to understand the implications of participation, an expectation to deliver at this hospital, and an intention to remain in Western Australia in the coming years such that childhood follow up was feasible. The study was approved by the Institutional Ethics Committee.

To see if the study sample represented the population, records were maintained on all pregnant women attending the antenatal clinics during a 6-month period mid-way through the study. At these 131 clinic sessions, 1420 women were new attenders of whom 510 (36%) were >20 weeks gestation, 117 (8%) were ineligible because of language difficulties, 60 (4%) planned to deliver elsewhere, 26 (2%) had psycho-social problems which precluded long-term follow-up, and 707 (50%) met the recruitment criteria: of these 633 (90%) agreed to participate.

Women were enrolled by one of three research midwives. Written consent was obtained, and a questionnaire completed with assistance from the midwife. This questionnaire contained 108 items enquiring about the woman's social and economic circumstances, lifestyle, past medical history, and environmental exposures. A second questionnaire was then given to the woman to be completed by her partner. This questionnaire contained 30 items enquiring about his physical size, education, occupation, and environmental exposures.

Randomisation and patients

After completion of her questionnaire, the woman was allocated to a group by a sealed-envelope technique prepared in blocks of 20 with computer-generated random numbers. The intensive group had ultrasound imaging and Doppler flow studies at approximately 18 weeks gestation and then at 24, 28, 34, and 38 weeks. Those allocated to the regular group were given an appointment for an ultrasound examination at 18 weeks, and any further scans were conducted only at the request of a clinician. Results of all ultrasound and Doppler flow studies were shown to the women and records were placed in the hospital chart. At 34 weeks gestation women in both arms of the study were asked to complete a further questionnaire to provide information on exposures between 18 and 34 weeks.

Ultrasound studies

Ultrasound examinations were all done by a qualified sonologist or sonographer with one of two General Electric 3600 machines (Milwaukee, USA) with 3·5 MHz linear array and 5MHz sector transducers. Measurements were made of the fetal biparietal diameter, occipitofrontal diameter, head circumference, abdominal circumference, and femur length. The amniotic fluid volume was assessed subjectively and classified into one of five categories. Placental morphology and location were described. The gestational age was calculated from the date of the last normal menstrual period in those women who were certain of this date and in whom that estimation did not differ by more than seven days from the estimation by biometry at 18 weeks. In other cases the gestational age was estimated by biometry at 18 weeks. After the ultrasound, each woman in the intensive group had a further examination to calculate the amniotic fluid index and to locate the umbilical cord and placental site (Aloka SSD-256, Tokyo, Japan). Doppler flow-velocity waveform studies were then done with a spectrum analyser (Medasonics SP25A: Mountain View, California) and a D10 bi-directional continuous wave Doppler system (total power output 3 milliwatts, spatial peak temporal average 25 milliwatts/cm²).[10] Systolic/diastolic ratios were calculated from waveforms obtained from an umbilical artery and an arcuate artery within the placental vascular bed.

Outcomes

Details of pregnancies, deliveries, and neonatal outcomes were taken from hospital notes. The allocation of each newborn to birthweight percentiles was done with locally-derived charts which allow for maternal height, parity, and fetal sex.[12] Poor obstetric history was defined as three or more first-trimester abortions, one or more second-trimester abortions, a perinatal death or a preterm birth. Obstetric intervention was defined as induction of labour or elective caesarean section. Information was collected on all ultrasound examinations, including those done at other centres prior to enrolment. Smoking was categorised by cigarettes smoked each day: 0, 1–5, 6–10, 11–15, 16–20, and >20. Socio-economic class was assessed by maternal and paternal levels of education, employment, family income, and marital status.

Statistical analysis

Power calculations estimated that a sample size of 2800 women would have a 90% power to detect a difference in the duration of

	Intensive	Regular	p
n	1415	1419	
Age (years)	27·4 (5·9)	27·3 (6·0)	0·83
Nulliparous	685	692	0·85
Poor obstetric history	243	249	0·80
Smoking at 18w	369	395	0·31
No of imaging studies per pregnancy			<0·001
1	43	797	
2	25	381	
3	57	130	
4	196	68	
5	821	29	
6	219	11	
>6	54	3	
Ultrasound at 18 weeks			
Days since last menstrual period	128·2 (4·68)	127·9 (4·74)	0·23
Biparietal diameter (mm)	42·2 (2·89)	42·1 (2·94)	0·31
Occipito-frontal diameter (mm)	52·9 (4·07)	52·8 (4·49)	0·71
Abdominal circumference (mm)	134·6 (11·58)	134·3 (11·24	0·46
Femur length (mm)	26·9 (2·67)	26·9 (2·72)	0·79
Fetal heart rate monitoring			
No of pregnancies	632	630	0·97
Median per pregnancy	2 (1–4)	2 (1–4)	0·39
Outcome			0·76
Abortion <20w	14	15	
Termination <20w	3	4	
Stillborn	10	12	
Born alive	1375	1368	
Lost to followup	13	20	
Labour onset			0·86
Nil	152	160	
Spontaneous	774	770	
Induced	459	450	
Preterm birth	113	123	0·49
Duration of neonatal stay (days)			
All babies	5 (4–6)	5 (4–6)	0·26
Babies >37 wks	5 (4–6)	5 (4–6)	0·27

Mean (SD) or median (interquartile) range.

Table 1: **Pregnancies, ultrasound, and fetal heart rate monitoring**

neonatal stay of 0·25 days in those who delivered at term ($\alpha = 0{\cdot}05$; SD = 2 days), and a power of 80% to detect a reduction in the preterm birth rate from 7% to 4·5%. Differences between the groups were tested by the t-test for independent parametric variables, Fisher's exact test for categorical variables with only two levels, Pearson χ^2 for those with more levels, and Mantel-Haenszel χ^2 for ordinal variables. Cohort relative risks with 95% confidence intervals were used to quantitate dichotomous outcome variables. Logistic regression modelling was done with the binary outcome of assignment/non-assignment of infants' size to being <3rd or <10th centile on the growth charts. Models were fitted by the maximum-likelihood method. Regression diagnostics[13] were used to quantify the effects of influence points on the fit.

Results

Outcome information was available for 2801 of 2834 women (99%) with single pregnancies. 13 were lost to follow-up in the intensive group of the trial and 20 in the regular. 114 (intensive 50, regular 64) women delivered in hospitals other than the King Edward Memorial, and their outcomes were still assessed. Of the 2900 women enrolled in the study, 66 had a multiple pregnancy. Of the rest, 1415 women were randomised to the intensive group of the trial, and 1419 to the regular.

The groups were comparable for maternal age, height, pre-pregnancy weight, marital status, race, parity, poor obstetric history, and smoking practices. The male partners in the two groups were also comparable (for the 80% on whom data were obtained), in height, weight and smoking practices. The groups were also comparable for the proportion of women with hypertension, diabetes, pre-labour rupture of membranes, preterm labour, stillbirths, the number admitted to hospital antepartum, onset of labour, and caesarean section rates. A written diagnosis of intrauterine growth restriction was observed more frequently in the medical records of women in the intensive group than in the regular group (relative risk 2·07; 95% CI 1·34 to 3·21).

Details of the ultrasound and electronic fetal heart rate monitoring studies are shown in table 1. When scanned at approximately 18 weeks gestation, the groups were similar both in mean gestational age as calculated from the date of the last normal menstrual period and in fetal biometry. Duration of neonatal stay (figure) and the rate of preterm birth, which were the principal end points of this trial, were similar in the two groups. There were also no differences between the groups in Apgar scores, cord arterial blood-gas values, frequency and type of neonatal resuscitation, proportion and duration of admissions to the neonatal intensive care unit, requirements for ventilation and oxygen, and the proportions with hyaline membrane disease, intraventricular haemorrhage, seizures and broncho-pulmonary dysplasia. Gestational age at birth and the proportions and types of congenital abnormalities were similar in the two groups. There were 10 neonatal deaths in the regular group and 3 in the intensive. Of the 10 in the regular group, 5 died of lethal congenital abnormalities and

Variable	Birthweight category	
	<3rd centile	<10th centile
Allocation to intensive arm of trial	1·84 (1·17 to 2·89)	1·46 (1·14 to 1·87)
Obstetric intervention	2·65 (1·69 to 4·17)	1·36 (1·06 to 1·75)
Advancing gestational age (per week)	0·79 (0·74 to 0·84)	0·86 (0·82 to 0·90)
Increasing smoking usage (per category)	1·34 (1·17 to 1·53)	1·29 (1·19 to 1·40)
Increasing maternal age (per year)	1·04 (1·00 to 1·08)	1·02 (1·00 to 1·04)

Table 2: **Adjusted odds ratios (95% confidence intervals) derived from multiple logistic regression analysis for variables shown to have independent effects on birthweight category**

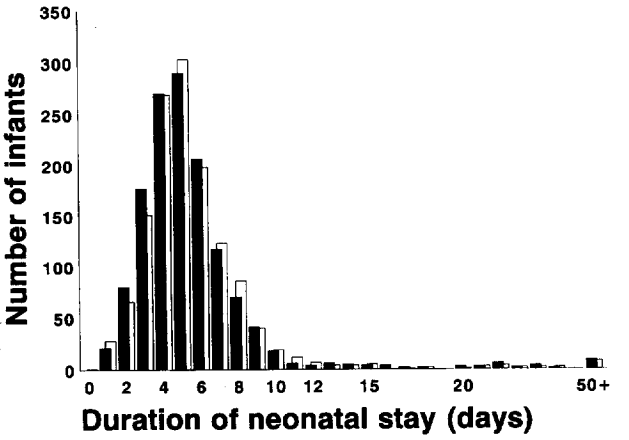

Figure: **Duration of neonatal stay in days: intensive group in black**

the remainder after preterm birth between 22 and 29 weeks gestation. In the intensive group, 3 neonatal deaths were due respectively to a motor vehicle accident, preterm birth at 22 weeks gestation, and a lethal congenital abnormality. None of the 13 neonatal deaths followed failure to diagnose fetal growth restriction. (Detailed information on the patients and pregnancy outcomes can be obtained from the corresponding author or *The Lancet*).

The proportion of liveborn infants with birthweights <10th centile was greater in the intensive group of the trial (relative risk 1·35; 95% confidence intervals 1·09 to 1·67; $p = 0{\cdot}006$) as was birthweight <3rd centile (relative risk 1·65; 95% confidence intervals 1·09 to 2·49; $p = 0{\cdot}020$). The mean birthweight in the intensive group was 25 g less than in the regular group, although this difference was not statistically significant. Multiple logistic regression analyses determined the effect of group allocation with other factors which may influence fetal growth (table 2). Statistically significant and independent effects on the probability of birth weight <3rd centile were observed for allocation to the intensive arm of the trial ($p = 0{\cdot}009$), gestational age at birth ($p < 0{\cdot}0001$), smoking practice ($p < 0{\cdot}001$), obstetric intervention ($p < 0{\cdot}001$) and maternal age ($p = 0{\cdot}035$). Analysis for the probability of birthweight <10th centile showed the same variables to have significant effects and the adjusted odds ratio (95% confidence interval) for allocation to the intensive arm was 1·46 (1·14 to 1·87). If obstetric intervention was considered as an outcome rather than a confounding factor, removal of this variable from the model did not alter the coefficients of the other parameters.

Ultrasound scans were done during the first trimester prior to involvement in this research study in 137 women in the intensive arm and 132 women in the regular arm of the trial. When the number of scans in the first trimester was added to the logistic regression analyses, this co-variate was found to have no effect on the probability of birth weight <3rd and <10th centiles ($p = 0{\cdot}931$, $p = 0{\cdot}233$ respectively).

Discussion

The results suggest that a protocol of frequent ultrasound imaging and Doppler flow studies between 18 and 38 weeks gestation does not improve pregnancy outcome as measured by duration of neonatal stay, requirements for resuscitation, and events in the neonatal nursery. There were 3 neonatal deaths in the intensive arm and 10 in the

regular arm with all deaths in the regular arm resulting from congenital abnormalities or preterm birth. We consider the difference in neonatal deaths most likely resulted from chance because of the small numbers involved, the lack of differences between the two groups in neonatal morbidity, and the absence of fetal growth restriction amongst the neonatal deaths in the regular arm. The finding of an increased proportion of infants in the intensive arm with birth weights under the 3rd and 10th centiles was accompanied by a trend towards a reduction in mean birth weight of approximately 25 g. Examination of percentile shifts indicates the effect was not a general decrease in growth of all fetuses, but rather a displacement of some babies into lower centile groups.

The randomisation was effective and there were no differences between the two groups in factors which are known to influence fetal growth. There also were no differences between the groups in duration of amenorrhoea or fetal biometry at the time of the first ultrasound examination at approximately 18 weeks gestation. Multiple logistic regression analyses showed that the increased proportion of growth-restricted fetuses in the intensive arm was not due to a chance effect from differential clustering within the two groups of maternal age, maternal height or parity, socio-economic class, smoking practices, obstetric history, or fetal sex. Obstetric intervention did not contribute to the differences in the two groups, thus precluding a possible effect of early delivery in those pregnancies in which altered fetal growth may have been diagnosed earlier by the frequent ultrasound examinations.

Authors of a previous study have suggested that a policy of routine ultrasound screening could enhance fetal growth by a reduction in smoking practice as women become more aware of their fetus;[8] however in the present study smoking rates ascertained by questionnaire at 18 and 34 weeks gestation did not differ between these two gestational ages in either group. The design of this study did not allow investigation of the dose response between the number of ultrasound examinations and fetal growth. Results of tests were revealed to clinicians as it was the purpose of the trial to investigate if this clinical protocol could be of benefit. Those pregnancies in which the fetus was believed to be growth restricted were often then referred for extra ultrasound examinations. Thus, any attempt to show a dose response would be biased.

An adverse effect of frequent ultrasound examinations on fetal growth is biologically plausible.[14,16] In monkeys, Tarantal and Hendrickx[17] observed a significant reduction in mean birthweight after frequent prenatal ultrasound examinations with equipment and techniques comparable to those employed in clinical practice. The investigators have since repeated these studies and reproduced their original findings.[18] Evaluations of an effect on fetal growth in humans from retrospective case series and case-control studies have suggested there is no effect, but the findings are limited by uncertainty about gestational age at the time of birth in the unexposed pregnancies, the criteria by which controls were chosen, and the small or uncertain number of scans performed in the exposed cases.[19] Retrospective studies, have not had the power to detect alterations in fetal growth of the magnitude observed in our study. To the best of our knowledge, there have been no controlled trials in humans designed specifically to investigate the safety of ultrasound. Plans by the British Medical Research Council for such a study were abandoned.[20] Several randomised controlled trials of the use of ultrasound in pregnancy have been reported, but in each the purpose was to investigate either a policy of routine ultrasound scanning when compared with a policy of clinical examination only,[1,5,7,8] of concealing the results of the test in the control group,[6,21] or of an additional scan during the third trimester.[4] Interpretation of any effect of routine ultrasound in most of these studies is limited by the lack of ultrasound examination of the control group, rendering gestational age assessment less accurate than in the intervention group. In the present study, each woman in the control group was allocated to receive a single ultrasound imaging examination at 18 weeks gestation in order to ensure that ascertainment of gestational age in the two groups was identical. Moreover, in previous trials only one or two scans were done, rendering any biological effect of ultrasound difficult to identify. Recently, Davies and co-workers[22] reported a randomised controlled trial of more than 2000 women in which a policy of routine continuous wave Doppler flow studies at 19–22 and 32 weeks gestation, with additional Doppler studies in the 15% of cases deemed to be at high risk, was compared with standard antenatal care which included an imaging study at 19–22 weeks. The proportion of infants with birthweight < 10th centile was similar in the two groups, indicating that the effect on fetal growth observed in our study was not evident in a similar trial in which the number of ultrasound examinations was much less.

Our findings suggest that five or more ultrasound imaging and Doppler flow studies between 18 and 38 weeks gestation, when compared with a single imaging study at 18 weeks gestation, increases the proportion of growth-restricted fetuses by about one third. It must be appreciated, however, that the purpose of this study was to investigate another hypothesis and it remains possible that the effect on birthweight percentiles was due to chance alone because this was not the principal endpoint under investigation. Nevertheless, our analyses have been unable to identify any other factors which could explain the observed effects on fetal growth. A large randomised controlled trial is now required which has been designed specifically to investigate the effects of ultrasound exposure on fetal growth. Such a study would appear to be ethical because the results of the present study do not indicate that any alteration in fetal growth is accompanied by excess neonatal morbidity or mortality. In the meantime it would seem prudent to limit ultrasound examinations of the fetus to those cases in which the information is likely to be of clinical importance.

We acknowledge the contribution of eight midwives: Mrs Pamela Stephenson, Mrs Cheryl Mayes, Mrs Catrina Hall, Mrs Michelle O'Dea, Mrs Karen Reid, Mrs Helen Fisher, Mrs Jacqueline Graham, and Mrs Barbara Chester. Ultrasound imaging was done by members of the KEMH Ultrasound Department including Dr John Phillips, Mrs Rae Roberts, Mrs Sarah Court, and Mrs Val Burnaby. Computer support was ably given by Mr Dean Diepeveen and Professor Ian James of Murdoch University. Acoustic output of the Doppler system was determined by Mr Keith Jones and Mr Andrew Campbell of the Royal Perth Hospital Physics Department. Secretarial support was provided by Mrs Robyn Pickering. We also wish to acknowledge with gratitude the staff of KEMH and the women and families of Western Australia. Supported by grants from the Raine Research Foundation of the University of Western Australia, National Health and Medical Research Council of Australia, and The King Edward Memorial Hospital Research Foundation.

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Impact of clinical trials on clinical practice: example of thrombolysis for acute myocardial infarction

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Summary

Little is known about incorporation of new knowledge from randomised clinical trials into clinical practice. Thrombolytic therapy was shown to reduce the mortality of acute myocardial infarction in several large trials published during 1986–88. To examine the effect of these data on clinical practice, we analysed the supply of thrombolytic drugs in a representative English region (population 4·7 million) in 1987–92.

During the study period there were over 10 000 hospital admissions per year in the region for acute myocardial infarction. From a very low initial level, thrombolytic drug use rose slowly for several years after publication of the trial results and reached a plateau in 1991–92. Rates of use per 1000 patients admitted with myocardial infarction varied almost six-fold between districts in 1989–90 and over two-fold in 1991–92. Level of use attained by districts in the latter period was strongly associated with the extent of their previous participation in multicentre trials of thrombolysis ($p = 0·003$); we estimate that 35–50% of patients admitted with acute myocardial infarction were receiving thrombolytics. The full potential of thrombolytic treatment has still not been achieved in routine care and the limiting factors need to be defined.

Lancet 1993; **342:** 891–94

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Introduction

Implicit in the design of a therapeutic trial is the supposition that a favourable result will modify the usual care of patients with the condition under study. However, the extent and the speed of the process of generalisation have been little studied. Development of intravenous thrombolytic treatment for acute myocardial infarction has provided a unique opportunity to examine the translation of new therapeutic knowledge into clinical practice for several reasons: (*a*) evidence of efficacy from a series of large well-conducted trials[1–6] is unusually strong and precise; (*b*) trial data were published over a very short time (1986–88); (*c*) data were widely circulated internationally (all reports were published in *The Lancet*) and were discussed extensively in both the medical and the lay press; (*d*) results led to rapid acceptance by physicians of the principle of thrombolytic therapy for acute myocardial infarction;[7,8] (*e*) the potential impact of this new treatment is substantial (reduction of about 25% in 5-week mortality). Although failure to adopt thrombolysis to the full has large public health implications, data from Europe[9,10] and North America[11] suggest that under 50% of suitable patients are receiving such therapy. Estimates of use have not been based on random or complete samples and are likely to have been biased upwards by over-representation of units with a research interest in myocardial infaction.

Consequently, we carried out an ecological study in a regional population of 4·7 million during the period 1987–92 to (*a*) define the time course of adoption of thrombolysis in response to publication of the trial data (*b*) examine the extent of, and reasons for, differences in