analogous results from research into schizophrenia[24]) but all participants who completed the experimental treatment reported treatment gains. The effects of the experimental treatment were large and may have been reduced because some patients in the control group will have probably tried to recognise prodromal symptoms of relapse on their own.[10]

The experimental treatment does not require a skilled therapist, but attention to detail is essential to identify accurately the nature and timing of prodromal symptoms of manic relapse. Cost effectiveness studies of the identification of manic prodromes followed by early treatment are required before the intervention is systematically introduced into the NHS.

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Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study

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Abstract

Objective To investigate whether maternal anxiety in the third trimester is associated with an increased uterine artery resistance index.

Design Cohort based study.

Subjects 100 pregnant women, with a mean gestation of 32 weeks.

Outcome measures Self rating Spielberger questionnaire for state anxiety and trait anxiety, and uterine blood flow waveform patterns as assessed by colour Doppler ultrasound.

Results A significant association was found between uterine artery resistance index and scores for both Spielberger state anxiety and trait anxiety ($r_s = 0.31$, $P < 0.002$ and 0.28 $P < 0.005$ respectively). Women with state anxiety scores > 40 ($n = 15$) had a higher mean uterine resistance index than those with scores ≤ 40 (mean difference with mean resistance index 24%, 95% confidence interval 12% to 38%; $P < 0.0001$). Similarly, women with trait anxiety scores > 40 ($n = 32$) had a higher mean resistance index than those with scores ≤ 40, although to a lesser extent. The presence of notches in the waveform pattern produced by uterine artery blood flow was found in 4/15 (27%) women with high state anxiety scores compared with 4/85 (5%) with low anxiety scores ($P < 0.02$).

Conclusions This study shows an association between maternal anxiety in pregnancy and increased uterine artery resistance index. It suggests a mechanism by which the psychological state of the mother may affect fetal development, and may explain epidemiological associations between maternal anxiety and low birth weight. The influence of maternal anxiety may be one mechanism by which

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the intrauterine environment contributes to later disease in offspring.

Introduction

The belief that a mother's psychological state can influence her unborn baby exists in most societies.[1] Some studies have shown that babies of stressed or anxious mothers have a significantly lower average birth weight for gestational age and tend to be born early.[2-5] In one large case-control study, the magnitude of the effect of stress on birth weight was similar to that found in the offspring of mothers who smoked.[6] As low birth weight seems to be associated with health problems in later life—for example, hypertension and ischaemic heart disease—this is of concern.[7] Ultrasound studies have shown that fetal behaviour is affected by maternal anxiety.[8 9] Animal studies have also shown that when the mother is stressed during pregnancy, birth weight is reduced and the behaviour of the progeny is permanently affected.[10 11]

There are several mechanisms by which maternal stress or anxiety might affect the fetus. Increased concentrations of hormones in the mother may be transported directly across the placenta.[12] Blood flow to the baby may also be impaired through the uterine arteries. Such an effect has been shown in primates, but has not yet been studied in humans.[13] We tested the hypothesis that anxiety in pregnant women is associated with abnormal blood flow in the uterine arteries. This was assessed by using colour Doppler ultrasound to both measure uterine artery resistance index and to detect the presence of notches in the waveform pattern produced by uterine blood flow (fig 1). A notch indicates particularly high resistance to blood flow. These variables have previously been associated with adverse obstetric outcome, particularly fetal growth restriction and pre-eclampsia.[14-16]

Subjects and methods

Subjects

Between April and December 1996, we asked 182 pregnant women at parentcraft classes if they would agree to participate in our study. Overall, 119 women with singleton pregnancies between 28 and 32 weeks of gestation agreed to participate within the next four weeks. Women who refused to participate did so mainly because of a lack of a mutually convenient appointment time; the proportion of these women (n=63) with pre-eclampsia (n=3) and small for gestational age babies at birth (<5th centile; n=3) was similar to the final cohort. We obtained informed written consent from each woman. We excluded women on the basis of the following criteria: *(a)* medical disease, including known pre-eclampsia or antepartum haemorrhage, *(b)* smoking, *(c)* previous adverse obstetric outcome, such as preterm delivery and small for gestational age baby, *(d)* assisted conception, *(e)* abnormal volume of amniotic fluid or abnormal velocity waveforms from the umbilical artery, *(f)* known small for gestational age fetus (<5th centile) on a previous scan, and *(g)* multiple pregnancy. Outcome data were obtained from the hospital obstetric database. Seven women were subsequently excluded from data analysis because of incomplete questionnaires or unclear uterine velocity waveforms. Overall, 100 women met the inclusion criteria.

Questionnaires

Immediately before Doppler ultrasound, the women completed two questionnaires. The first was a simple questionnaire to ascertain their history of emotional problems, major life events in the past 3 months, and alcohol intake (none consumed more than one unit a day). The second was the Spielberger questionnaire, which comprises two parts measuring both state anxiety and trait anxiety.[17] For state anxiety, subjects are asked how they feel at the time of being questioned, and for trait anxiety, subjects are asked how they feel generally. Before the study, a cut off point of scores >40 was selected for both state anxiety and trait anxiety.[18]

Doppler ultrasound

We recorded the Doppler flow velocity waveforms using an Acuson XP 10 or Sequoia ultrasound machine (Acuson, CA, USA) with a 3.5 or 5 MHz probe. These were later analysed by the same operator (JT), blind to the questionnaire results. Colour Doppler ultrasound was used to identify the main branch of the uterine artery at its junction with the internal iliac artery, from where we obtained blood flow velocity waveforms. Waveforms were recorded from both uterine arteries, and from the fetal middle cerebral artery and umbilical artery in standard fashion. We derived the resistance index for the uterine arteries (fig 1), and the pulsatility index (A − B/mean waveform height (fig 1) for fetal vessels, from five consecutive uniform waveforms. The mother's heart rate at the time of scanning
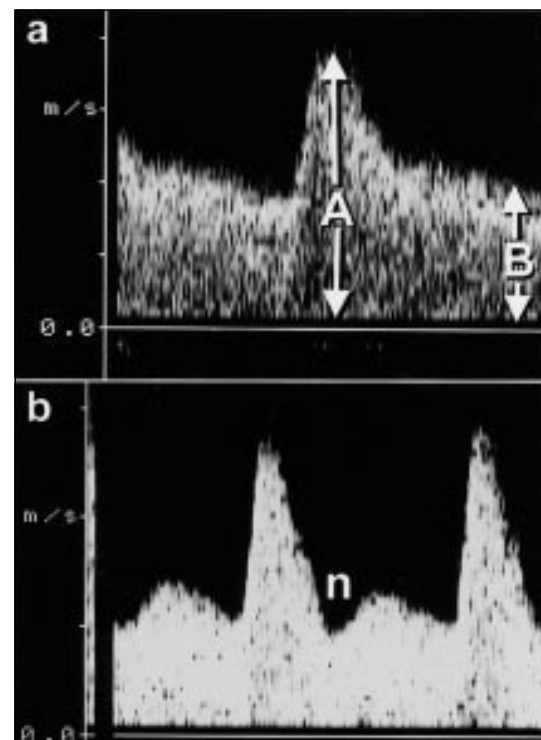
Fig 1 Uterine artery waveforms: (a) normal, (b) abnormal. Resistance index=(A–B)/A. A notch (n) indicates particularly high resistance to blood flow

was similarly derived. The presence or absence of a notch in each uterine waveform was noted, and subjects were considered positive if the notch was present unilaterally. The coefficient of variation for the repeated measurement of resistance index was 6%. All 100 women had complete Doppler ultrasound studies of the uterine artery with full data for mean resistance index, maximum resistance index, and notching. Only 84 women had full fetal Doppler ultrasound studies; complete fetal Doppler data were obtained from 13/15 women with high state anxiety scores (high anxiety group) and from 71/85 women with low state anxiety scores (low anxiety group).

Statistics

Mean resistance index was calculated as the mean value from both left and right uterine arteries. Maximum resistance index was the maximum of the mean values obtained from either artery. Continuous variables were tested for normality, and variables that were not distributed normally were transformed appropriately. The following tests were used as appropriate: Student's t, Mann Whitney U, Fisher's exact, and Wilcoxon matched pairs tests. All the tests were two tailed.

Results

In the final cohort of 100 women, the state anxiety score was lower than the trait anxiety score: median (range) 28.5 (20-61) versus 36 (20-67) (P < 0.001). Fifteen women scored > 40 for state anxiety, and 32 women scored > 40 for trait anxiety.

A significant association was found between maximum resistance index and both state anxiety scores ($r_s = 0.31$, P < 0.002) and trait anxiety scores ($r_s = 0.28$, P < 0.005), and between mean resistance index and both state anxiety scores ($r_s = 0.28$, P < 0.005) and trait anxiety scores ($r_s = 0.21$, P < 0.03). Figure 2 shows the data for maximum resistance index.

When the groups were dichotomised, using the predetermined cut off point of a score of > 40, women in the high state anxiety group had significantly worse uterine velocity waveforms than those in the low state anxiety group, whether considered as mean resistance index, maximum resistance index, or notching (table); mean difference in mean resistance index 24%; 95% confidence interval 12% to 38%; P < 0.0001; and mean difference in maximum resistance index 23%; 10% to 37%; P < 0.0005. Using trait anxiety (> 40), there were also differences between high and low anxiety groups (mean difference in mean resistance index 13%; 4% to 23%; P < 0.005); and mean differences in maximum resistance index (mean increase 16%; 6% to 26%; P < 0.001). The 15 women who had the highest trait anxiety scores (12 of whom also had high state anxiety scores), had similar mean and maximum resistance indexes to the 15 women who had high state anxiety scores (0.56. and 0.63 respectively). Those women who had low scores for state anxiety but high scores for trait anxiety (n = 20) were not significantly different for mean or maximum resistance indexes from those women with low scores for both state anxiety and trait anxiety (n = 65).

We also compared the two state anxiety groups for the proportion of women with a resistance index of

Uterine Doppler ultrasound characteristics in 100 mothers with either low (≤40) or high (>40) Spielberger state anxiety scores. Values are geometric means (95% confidence intervals) unless stated otherwise

	Low anxiety scores (n=85)	High anxiety scores (n=15)	P value
Mean resistance index	0.47 (0.45 to 0.49)	0.58 (0.50 to 0.67)	<0.0001
Maximum resistance index	0.51 (0.49 to 0.54)	0.63 (0.56 to 0.71)	<0.0005
No (%) with mean resistance index ≥0.68	3 (4)	4 (27)	<0.01
No (%) with notching	4 (5)	4 (27)	<0.02

0.68 or above—that is, the upper limit of the 95% reference range for a mean gestation of 32 weeks.[19] In the most anxious group, 4/15 (27%) women had a mean resistance index ≥0.68 compared with 3/85 (4%) women in the less anxious group (P < 0.01) (table). Of the seven women with mean resistance indexes ≥0.68, six had high trait anxiety scores.

The group of women with a notch was overlapping but distinct from those with a resistance index ≥0.68. The group had a mean (SD) resistance index of 0.6 (0.1). The presence of a notch (unilateral or bilateral) was associated with state anxiety; 4/15 women in the high anxiety group had a notch compared with 4/85 women in the low anxiety group (P < 0.02). All but one of those with a notch had high scores for either state anxiety or trait anxiety. The remaining patient scored 20 (in effect zero) on both scales.

The best multiple regression model to predict mean resistance index comprised state anxiety scores (P < 0.001) and maternal heart rate (P < 0.02), whereas to predict maximum resistance index or notching, the best multiple regression model comprised only state anxiety scores (P < 0.01) for both.
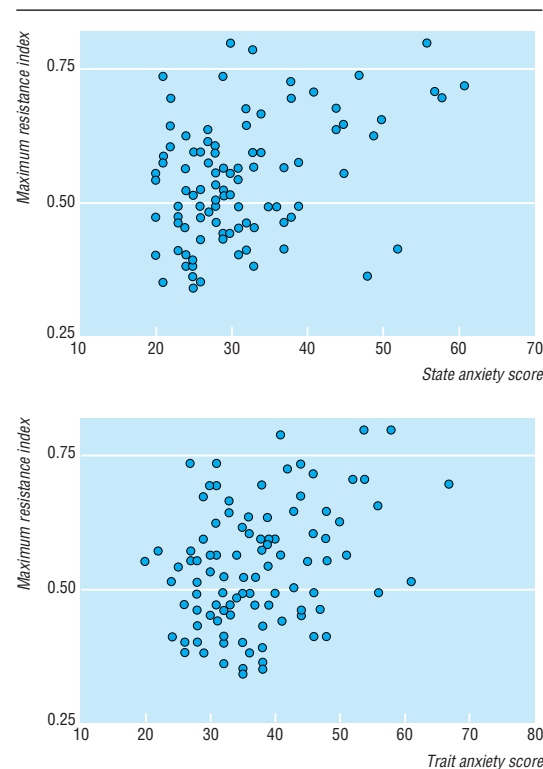
Fig 2 Correlation between maximum resistance index and scores for both state anxiety (r_s=0.31, P=0.00180) and trait anxiety (r_s=0.28, P=0.0048) in 100 pregnant women

No significant differences were found in the clinical variables studied between the high and low anxiety groups, whether divided by state anxiety or trait anxiety. For the mother these included age, maternal heart rate, parity, and emotional history or life events during this pregnancy. For the fetus they included birth weight, estimated fetal weight and gestational age at Doppler ultrasound, fetal heart rate, and pulsatility index of the umbilical and middle cerebral artery. All subjects were normotensive ($<120/90$) at the time of Doppler analysis. Four women developed pre-eclampsia before delivery, all in the low anxiety groups; one woman had a notch and high resistance index (mean 0.7), and the other three women had normal uterine waveforms. Six fetuses were small for gestational age at birth. The median mean resistance index value for these was 0.6 (range 0.42 to 0.73).

Discussion

This study shows an association between anxiety and a high resistance index whether analysed as continuous data (fig 2) or dichotomised (table). Women with increased anxiety are more likely to have abnormal variables for uterine artery blood flow than those with less anxiety, whether considered as mean resistance index, maximum resistance index, or notching. This association was more pronounced for state anxiety than for trait anxiety. There were, however, more women in the high trait anxiety group than in the high state anxiety group.

Furthermore those women with abnormal Doppler ultrasonograms were more likely to be anxious. All eight women with a notch had an abnormal score on the Spielberger questionnaire (0 scores often signify denial and an underlying psychopathology[20]). In addition, 6/7 women with resistance indexes ≥0.68—that is, the 95th centile—had high anxiety scores, four had high state anxiety scores, and six had high trait anxiety scores.

Women with high state anxiety scores had slightly, although insignificantly, faster heart rates. However, we used multiple regression to show that the association between mean resistance index and state anxiety score was not a confounding effect of maternal heart rate.

The 100 women we studied seem reasonably representative of a non-selected population. Seven had mean resistance indexes on or above the 95th centile, eight had notches (a similar freqency to that found in a large population study[16]), six had babies with birth weights at or below the 5th centile. In the general population about 30% of women score >40 for both state anxiety and trait anxiety.[21] We observed the same proportion for trait anxiety scores, but not for state anxiety scores. State anxiety scores were lower. It may be that pregnancy in itself was relaxing, at least in the middle of the third trimester in this cohort of women with no obstetric complications.

The Doppler ultrasound waveforms studied here predominantly represent downstream resistance, and not strictly blood flow. However, assuming a relatively stable cardiac output, they are a reasonable index of uterine blood flow. Studies on Doppler ultrasound of uterine arteries to predict impaired trophoblastic inva-sion have attempted to concentrate on the side supplying the placenta. In this study we have chosen to determine the mean of the resistance indexes on both sides of the uterus (mean resistance index), because ascribing placentation entirely to one side is necessarily artificial. As the highest resistance index (maximum resistance index) is the more abnormal, and possibly thus more clinically relevant, we also analysed this. Whether mean or maximum resistance index was used, the results were generally similar. Impaired uterine blood flow is generally considered a chronic phenomenon, predominantly due to failure of invasion of the placenta by the trophoblast in early pregnancy,[22] and abnormal patterns, either high resistance indexes or notching, are predictive of pre-eclampsia and intrauterine growth retardation.[16] This does not, however, exclude later changes in uterine blood flow, such as might be associated with transient changes in maternal hormone concentrations, as shown in animal models.[23] Indeed, exercise transiently increases uterine resistance indexes in pregnant women at around 34 weeks of gestation,[24] and treatment interventions can acutely improve blood flow.[25 26]

The hypothalamic-pituitary-adrenal axis may be involved in the altered blood flow pattern described here,[27] but an obvious candidate for mediator is noradrenaline. High scores for state anxiety are associated with increased plasma noradrenaline concentrations.[28] Also, infusion of noradrenaline decreases uterine blood flow, both in pregnant sheep and pregnant guinea pigs.[23 29] In fact, in sheep, reproductive tissues (including the uterus) were more sensitive to the vasoconstrictive effects of noradrenaline than were other body tissues.[29] It may be that in times of stress the mother has evolved to protect herself at the expense of her fetus.[30]

We do not know whether the associations between anxiety and Doppler ultrasonograms are acute or chronic. Although we found stronger associations for state anxiety than for trait anxiety, the top 15% of women with either score were largely the same patients, and had similarly abnormal waveforms. Further work is needed to determine whether overall anxiety during pregnancy or even before or at conception might affect uterine artery blood flow, or instead whether the association is only with the current

Key messages

- Women who were anxious during pregnancy had significantly abnormal patterns of blood flow through the uterine arteries

- Of the most anxious group, 27% had an increased resistance index of clinical concern, compared with 4% in the less anxious group

- The study did not establish whether the impaired blood flow was predominantly linked with state anxiety or trait anxiety

- The findings may help to explain previous studies that have linked stress or anxiety in pregnancy with small for gestational age babies

emotional state. It is also possible that there is some underlying factor that causes both increased anxiety and diminished trophoblastic invasion. It is unlikely that the women in our study had reason to be concerned about the progress of their pregnancy, as we excluded those with pre-eclampsia or fetal growth retardation known before Doppler ultrasound.

Although there are many contributors to fetal growth and birth weight, reduced blood flow through the uterine arteries could partially explain why women who are anxious during pregnancy tend to have smaller babies. It is also possible that this mechanism is related to some of the findings by Barker,[7 31] which have linked low birth weight to a later predisposition to coronary heart disease.

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Endpiece
Alternative definitions

Die: The singular of dice. We seldom hear the word, because there is a prohibitory proverb, "Never say die."

Ambrose Bierce, *The Cynic's Word Book* (1906), subsequently titled *The Devil's Dictionary*

Notice of inadvertent duplicate publication

The *BMJ* regrets that the paper "Diabetes mellitus and raised serum triglyceride concentration in treated hypertension—are they of prognostic importance? Observational study" by O Samuelsson et al (14 September 1996;313:660-3) was substantially similar to a paper published in the *Journal of Internal Medicine* entitled "The role of diabetes mellitus and hypertriglyceridaemia as coronary risk factors in treated hypertension: 15 years of follow up of antihypertensive treatment in middle aged men in the Primary Prevention Trial in Göteborg, Sweden" (1994;235:217-27). The statistical evaluation is more thorough in the *BMJ* paper, but the articles present essentially the same data on the same patients. However, we were not told of the existence of the earlier paper, in contravention of our instructions to authors and of internationally agreed guidelines. Professor Samuelsson has apologised for not making us aware of the possible duplication.