Associations of maternal psychological factors with umbilical and uterine blood flow

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Abstract
Objective. Alteration to blood flow in the maternal–foetal compartment has been proposed as a mechanism underlying maternal psychological effects on pregnancy outcomes. This study characterised the progression of umbilical and uterine blood flow resistance in healthy pregnancies and evaluated concurrent and longitudinal associations with maternal anxiety and other psychological factors.
Methods. The study assessed participants (n = 107) at five visits spanning 24–38 weeks gestation. The resistance index (RI) in the uterine and umbilical arteries was measured with Doppler ultrasound. Maternal psychological function was assessed using validated, self-report instruments.
Results. Hierarchical linear modelling revealed that uterine and umbilical RI decreased during the second half of gestation, and that uterine RI was lower in nulliparous women. Few concurrent associations emerged between psychological factors and RI. Longitudinal analyses determined that psychological well-being was associated with decreased left uterine artery RI, and psychological distress was associated with lower right artery RI.
Conclusions. Although uterine artery resistance was modestly associated with the maternal psychological milieu during gestation, our findings do not indicate an association between increased maternal distress and decreased RI. Thus, this study fails to affirm a key component of the hypothesised relation of maternal stress to foetal outcomes via vasoconstriction.

Keywords: Perinatal mental health, pregnancy, Doppler ultrasound, blood flow resistance

Introduction
A woman’s psychological state during pregnancy has long been thought to influence the health and well-being of her offspring. However, empirical findings present a mixed picture of the potential effects of maternal antenatal psychological distress. Maternal antenatal depressive symptoms, anxiety and perceived stress have been associated with low birthweight and spontaneous preterm birth in some studies [1–5], but others found no adverse effects of antenatal psychological distress on birth weight, gestational age at delivery, obstetric complications or child development at age 2 [6–10]. Identification of pathophysiology by which maternal psychological factors may influence foetal outcomes is important to understanding such variation in outcomes.
Alteration to blood flow in the maternal–foetal compartment is commonly proposed as a putative mechanism underlying maternal psychological effects on pregnancy outcomes, primarily as a result of vasoconstriction associated with the stress response [2,4,11,12]. Doppler ultrasonography of the uterine and umbilical arteries offers a non-invasive method for studying foetal blood flow. Elevated Dopplers are also associated with maternal complications, including pre-eclampsia and foetal intrauterine growth restriction [13]. To our knowledge, only four studies have evaluated the relation of maternal psychological
factors to maternal blood flow to the foetus, and these have generated mixed results. Teixeira et al. [14] reported that both state and trait anxiety scores were associated with increased uterine artery resistance (mean of right and left arteries) in a sample of 100 healthy pregnant women at 32 weeks gestation. However, Kent et al. [15] did not find a significant association between self-reported anxiety and uterine artery resistance among 96 healthy pregnant women at 20 weeks gestation. In a study of 37 healthy pregnant women at term, women with high self-reported trait anxiety had higher pulsatility index (PI) values in the umbilical artery than their low trait anxiety counterparts, as well as lower PI values in the foetal middle cerebral artery and lower cerebro-umbilical PI ratios [16]. These studies are limited by cross-sectional designs in which anxiety and blood flow were measured at a single point during the second or third trimester of pregnancy.

More recently, Maina et al. [17] conducted a prospective study that included uterine and umbilical artery Doppler velocimetry measures at 20 and 34 weeks gestation. Three groups of pregnant women were evaluated: women with a diagnosis of depression and/or anxiety disorder (n = 20), women with at least one severe life event during pregnancy or in the year prior (n = 20) and women without psychiatric diagnoses or stressful life events (n = 40). There were no significant differences in uterine or umbilical Dopplers among the three groups. This study has the advantages of a prospective design and inclusion of both uterine and umbilical Doppler measures. However, the study reported only percentages of abnormal Doppler values and did not evaluate relative resistance or pulsatility values, which may have obscured more subtle differences.

The limited literature on maternal psychological state and foetal blood flow also has not addressed two other key aspects of maternal psychological function. The first is the role of pregnancy-specific stressors, which contribute to the total burden of distress and are generally unmeasured [18,19]. Second is the possible salutary influence of positive maternal emotions, which have been associated with positive antenatal health behaviours and more favourable birth outcomes [20].

This study addressed the limitations of previous studies using a prospective, longitudinal design with repeated assessment of uterine and umbilical Doppler velocimetry collected concurrently with maternal psychological measures, both positive and negative. We hypothesised that indicators of maternal psychological distress would be associated with increased vascular resistance. Based on the evidence cited above for a link between positive maternal emotions and favourable birth outcomes, we also hypothesised that indicators of maternal psychological well-being would be associated with decreased resistance.

Methods

Sample

Participants were 120 normotensive, non-smoking women with normally progressing singleton pregnancies. Participants were self-identified volunteers recruited via local university and hospital-based advertisements. Women with medical conditions that complicate pregnancy (e.g. Type I diabetes) were not eligible to participate. Participants with gestational diabetes (n = 6), current treatment for depression (n = 6) or both (n = 2) were excluded from the analysis resulting in a sample of 107. Accurate dating of the pregnancy, based on early first trimester pregnancy testing or examination and generally confirmed by early ultrasound was required (mean gestational age at pregnancy detection = 4.8 weeks; sd = 1.2). The sample represents a relatively stable population of well-educated (mean years education = 17.2 years, sd = 2.1), mature (mean age = 31.2, sd = 4.6), married (90.7%) women. Most were non-Hispanic white (79.4%); the remainder was African-American (13.1%) and Hispanic or Asian (7.5%). Fifty-six (52.3%) of the foetuses were female, and this was the first pregnancy for 77 (72%) of the participants.

Data assessment and design

In order to fully represent the gestational age span from 24 to 38 weeks gestation, participants were stratified into three cohorts with staggered entry into the protocol between 24 and 26 weeks gestation and were tested in 3-week intervals. That is, data collection for the first cohort proceeded at 24, 27, 30, 33 and 36 weeks; the second at 25, 28, 31, 34 and 37 weeks; and the third at 26, 29, 32, 35 and 38 weeks. Data collection took place in a hospital setting. Study visits were scheduled at 1:00 pm or 3:00 pm, and women were instructed to eat 1.5 h prior to the visit but not thereafter. Women completed psychosocial questionnaires upon arrival. The local Institutional Review Board approved this research, and women provided informed consent.

Measures

Uterine and umbilical artery blood flow was measured with Doppler ultrasound (Picus, Pie Medical) using a 3.5-MHz transabdominal probe by a single, experienced operator (K.C.) with women in a supine position. Color Doppler imaging was used to locate the main branches of the right and left uterine arteries, and the Doppler gate was positioned close to their junction with the internal iliac artery. The angle of insonation was adjusted to maximise the systolic peak with an angle less than 35°. A series of three consecutive waveforms were recorded and traced.
A standard clinical indicator of arterial resistance (i.e. resistance index, RI) was calculated using values derived from the single best waveform. The umbilical artery was similarly imaged with color Doppler, and the RI was computed based on sampling at a distance from the placental and umbilical cord insertion site.

The psychosocial questionnaires were administered at each visit and included measures of general anxiety, depressive symptoms, emotional well-being and pregnancy-specific stress and uplifts. Anxiety symptoms were evaluated by the Spielberger Trait Anxiety Scales (Y-2; STAI) [21], one of the most extensively validated self-administered anxiety measures and the most commonly used measure of anxiety during pregnancy. This questionnaire includes twenty 4-point items; higher scores indicate greater trait anxiety. The STAI has been found to have strong psychometric properties, including a median alpha reliability coefficient of 0.90 [21]. Depressive symptoms were assessed using the Centre for Epidemiologic Survey Depression Scale (CES-D) [22]. The CES-D is a widely-used 20-item self-report measure of depressive symptomatology over the past week in which items are rated on a 4-point scale. The CES-D has been used in numerous studies of the perinatal period, and Cronbach $z$ results ranging from 0.83 to 0.88 reflect high internal reliability during pregnancy and postpartum [23–25]. Emotional well-being was assessed using the World Health Organisation Five Well-being Index (WHO-5) [26], a five-item self-report measure that has been shown to possess good psychometric properties [27–29]. Pregnancy-specific stress was assessed by a shortened form of the previously validated Pregnancy Experiences Scale (PES) [18]. The PES-Brief includes the 10 most frequently endorsed hassles and uplifts from the full PES, each rated on the original 4-point scale, and averaged. Higher values reflect greater perceived intensity of negative or positive feelings about the pregnancy. Comparable reliability and stability to the original have been demonstrated [30].

**Data analysis**

Descriptive analyses examining correspondence among Doppler values and with the psychological scales were based on correlation coefficients. Hierarchical linear modelling (HLM) was used to characterise change in RI from 24 to 38 weeks for the umbilical artery and uterine arteries. Restricted maximum likelihood (REML) was used in reporting model parameters when assessing the significance of the random effects; degrees of freedom were estimated using the Satterthwaite method. The 95% confidence interval (CI) for each fixed effect was calculated as its estimate $\pm 2$ standard errors. Random effects specified for cohorts and individuals were assessed (i.e. the covariance of scores at 38 weeks across cohorts and individuals). In the event that the estimate of the variance was very small and not statistically significant, we ignored the effect of between-cohort variance on the total variance and dropped it from the final model, whereas random effects that were statistically significant were retained in the final models. Thus, results reported were based on two-level HLM models with repeated measurements nested within individuals. A number of covariates at the individual level were evaluated as potential confounders for inclusion into the final HLM models.

Because data were collected at 15 successive gestational weeks, interpreting individual correlations between each psychological measure and the three Dopplers at each gestational week was not feasible. Instead, preliminary analyses were conducted by visit for each of the three sequential cohorts. For example, visit 1 includes data collected at 24, 25 or 26 weeks gestation. Because there is conceptual and empirical overlap between psychological constructs measured by these scales, composites were created to reduce the number of final HLM models and increase the stability of the estimates. The STAI, CES-D and PES-Brief Hassles values were separately standardised using $z$ scores at each time period and then summed to create a maternal distress composite. The same procedures were implemented with the WHO-5 and PES-Brief Uplifts values to create a maternal well-being composite. Composites were entered as predictors in separate HLM models. HLM analyses used the Mixed procedure in SAS version 9.2 (SAS Institute, Cary, NC).

**Results**

Participation rates were as follows: 102 (95.3%) at visit 1; 95 (88.7%) at visit 2, 90 (84.1%) at visit 3, 97 (90.7%) at visit 4 and 82 (76.6%) at visit 5. At each visit, some missing values were generated by an inability to obtain a sufficiently clear Doppler signal, resulting in additional slight variation in sample sizes over gestation. A single outlier value for right uterine artery RI was removed at visit 2.

**Longitudinal progression of blood flow resistance**

RI values within each artery displayed low to moderate consistency over the five visits: correlation coefficients ranged from 0.07 to 0.32 with an average correlation of 0.21 for the umbilical artery, from 0.05 to 0.44 for the right uterine artery (average association = 0.26), and from 0.16 to 0.44 for the left uterine artery (average association = 0.29). Intraclass correlation coefficients for measurements of
the umbilical, right uterine and left uterine artery RI values were 0.24, 0.27 and 0.27, respectively.

Foetal sex and maternal characteristics, including parity, mean arterial pressure (MAP), and maternal weight, were assessed as possible influences on RI. Parity was associated with right (estimate = 0.026, SE = 0.012, t = 2.09, p < 0.05) and left (estimate = 0.026, SE = 0.012, t = 2.3, p < 0.05) uterine RI values such that nulliparous women had lower uterine resistance than parous women. However, nulliparous women were also younger (t = -2.38, p < 0.05) and had higher MAP at three of the five visits. Umbilical RI was unrelated to these maternal characteristics or foetal sex. Parity (nulliparous versus parous) was controlled in longitudinal models.

HLM analyses controlling for parity indicated significant decline in RI for the umbilical artery (estimate = -0.008, SE = 0.001, t = -15.08, p < 0.0001), right uterine artery (estimate = -0.005, SE = 0.001, t = -5.59, p < 0.0001) and left uterine artery (estimate = -0.002, SE = 0.001, t = -2.72, p < 0.01) from 24 to 38 weeks. Figures 1 and 2 display RI values for the umbilical and uterine arteries, respectively, over time.

Association of maternal psychological factors and blood flow resistance: cross-sectional analyses

Associations between right and left uterine RI within women were fairly low (ranging from -0.07 to 0.37 with a mean association of 0.21), and preliminary analyses revealed different patterns of associations with psychosocial values. As a result, analyses evaluating the associations between psychological factors and RI were conducted separately for each side.

STAI, CES-D, WHO-5 and PES-Brief hassle scores were not correlated with umbilical or either uterine artery RI at any visit. PES-Brief uplifts were marginally associated with left uterine artery RI at visits 4 (r = -0.20, p = 0.07) and 5 (r = -0.21, p = 0.08). Correlations were also computed between these measures and averaged right and left uterine RI values to replicate reports from other studies that have used this approach; no significant associations were observed with any psychological factors.

Association of maternal psychological factors and blood flow resistance: longitudinal analyses

Longitudinal analyses were estimated using the two composite scales of maternal distress and well-being. Maternal distress and well-being were negatively correlated at each study visit: r = -0.54 (p < 0.0001) at visit 1, r = -0.49 (p < 0.0001) at visit 2, r = -0.64 (p < 0.0001) at visit 3, r = -0.60 (p < 0.0001) at visit 4 and r = -0.66 (p < 0.0001)
Discussion

This prospective cohort study of 107 singleton normally progressing pregnancies assessed the longitudinal progression of blood flow resistance from 24 to 38 weeks gestation and evaluated the associations of maternal psychological factors with blood flow resistance across that period. Decreases in umbilical and uterine artery resistance were observed with advancing gestation, consistent with a previous report [31]. A progressive decrease in blood flow resistance is consistent with the physiology of a healthy pregnancy: invasion of placental trophoblast cells causes progressive dilation in the maternal spiral arteries, decreasing resistance and facilitating transfer of oxygen and nutrients to the developing foetus [32,33]. Nulliparous women had lower uterine blood flow resistance than parous women, consistent with an earlier result generated between 18 and 23 weeks gestation [34]. The current findings confirm that persistent alterations to maternal vasculature are established in subsequent pregnancies and demonstrate that these remain in place throughout gestation.

Cross-sectional analyses did not reveal any significant associations between individual psychological scales and resistance, with the exception of marginal associations between pregnancy-specific uplifts and decreased resistance after 33 weeks. Averaging right and left RI values, as done in some prior studies [14,15,17], also yielded no significant associations at any visit. Our findings are consistent with those of Kent et al. [15], in which no association between maternal anxiety and uterine artery resistance at 20 weeks gestation was detected but in contrast to two other studies that reported modest cross-sectional associations, i.e. between anxiety at 32 weeks and averaged uterine artery resistance [14] and anxiety at term and umbilical pulsatility [16]. The current results generated from this prospective cohort raise questions about the replicability and generalisability of findings based on single psychological instruments assessed at a single gestational age.

More coherent findings were revealed when the longitudinal study design was used, and composite measures of psychological functioning were formulated. From a conceptual standpoint, analyses based on single instrument assessment of psychological functioning do not adequately capture how various types of emotional experience overlap and cohere. As predicted, maternal psychological well-being was associated with decreased resistance, although only in the left uterine artery. This suggests that a positive outlook during pregnancy confers a benefit to blood flow. This observation is bolstered by a finding that women who slowed their breathing more to an experimental relaxation manipulation had decreased...

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Note: Gestational age was centered at 38 weeks. Random effects specified for the models for the covariance of the intercept across individuals were all statistically significant with p < 0.0001.

*p < 0.05, **p < 0.01, ***p < 0.0001.
uterine artery resistance following the procedure [35]. Measurement instruments for positive emotions are much less developed than those for negative ones, and better understanding of the complex nature of the interface between maternal emotions and the physiology of pregnancy would be advanced by development of more sophisticated tools.

Maternal distress was also associated with resistance, but only in the right uterine artery, and the direction of association was counter to prediction. An adverse association between distress and uterine artery RI has only been reported in a single study, and that finding was limited to 32 weeks gestation [14]. We have no ready explanation as to why greater maternal distress is associated with decreased resistance. It is possible that greater antepartum emotionality in general, either positive or negative, may confer an advantage to blood flow. We are unable to determine whether the differential findings in the right and left arteries reflect true physiologic differences. Resistance values were generated while women were in a supine, not lateralised position, so it is possible that uterine blood flow characteristics were influenced as well by aortic or inferior vena cava compression. We did not document placental lateralisation, and since placental location lowers ipsilateral Dopplers, a bias towards right or left implantation in the sample as a whole may have introduced a source of confound.

This study has certain limitations. As we did not recruit women with psychiatric disorders, our findings may not generalise to psychiatric pregnant populations. In this study, psychological factors were assessed using self-report measures and were not evaluated with clinician ratings. Self-report ratings may reflect subjective response biases; however, recall bias is unlikely to have affected results given that participants were asked to report on emotional states over the past 1–2 weeks.

In summary, results suggest that the maternal psychological milieu during pregnancy exerts influence on uterine artery, but not umbilical, blood flow. Study strengths include the prospective longitudinal design with multiple antenatal assessments and measurement of both umbilical and uterine artery resistance as well as multiple maternal psychological indicators. Although the results are statistically significant, they suggest very modest associations. We believe the key implication of these findings is in disputing the assumption that documented associations between maternal distress and poor pregnancy outcomes, including growth restriction, are mediated by changes in blood flow. Findings in this study illustrate the complexity of the interface between maternal psychological function and the physiology of normal pregnancy, as well as limitations in the current knowledge base.

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References
Current knowledge on this subject

- Alteration in blood flow from mother to foetus has been proposed as a mechanism by which maternal psychological distress may influence pregnancy outcomes.
- Only four studies have evaluated the relation of maternal psychological factors to maternal–foetal blood flow, with mixed results.
- Previous research in this area has a number of limitations, including cross-sectional designs in most studies.

What this study adds

- This study used a prospective longitudinal design with multiple antenatal assessments, and it included measures of both umbilical and uterine artery resistance, as well as multiple maternal psychological indicators.
- Our findings suggest uterine artery resistance is modestly associated with the maternal psychological milieu during gestation.
- Findings do not indicate an association between increased maternal distress and decreased RI and thus do not support vasoconstriction as a compelling mechanism in translating maternal emotions to foetal growth or other aspects of development.