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Prenatal stress and hemodynamics in pregnancy: a systematic review

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Full title: Prenatal Stress and Hemodynamics in Pregnancy: a Systematic Review

Short title: Stress and Hemodynamics in Pregnancy

Abbreviations: BDI: Beck Depression Inventory; CES-D: Center for Epidemiologic Survey Depression Scale; CPR: cerebroplacental ratio; CRH: corticotrophin-releasing hormone; GHQ-28: General Health Questionnaire; HADS: Hospital Anxiety and Depression Scale; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for Depression; IES: Impact of Event Scale; K10: Kessler Psychological Distress Scale; MCA: middle cerebral artery; MINI: Mini International Neuropsychiatric Interview; PES-Brief: Pregnancy Experiences Scale; PI: pulsatility index; PSS: Perceived Stress Scale by Sheldon Cohen; RI: resistance index; S/D: systolic/diastolic ratio; SSRI: selective serotonin reuptake inhibitor; STAI: State-Trait Anxiety Inventory; UA: umbilical artery; UtA: uterine artery; WHO-5: World Health Organization Five Well-being Index

Key words: Blood flow, Doppler ultrasound, fetal well-being, hemodynamics, middle cerebral artery, pregnancy, pregnancy-specific stress, psychological distress, stress, umbilical artery, uterine artery

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Abstract

Purpose: Maternal prenatal stress is associated with preterm birth, intrauterine growth restriction, and developmental delay. However, the impact of prenatal stress on hemodynamics during pregnancy remains unclear. This systematic review was conducted in order to assess the quality of the evidence available to date regarding the relationship between prenatal stress and maternal-fetal hemodynamics.

Methods: The PubMed/Medline, EMBASE, PsycINFO, Maternity and Infant Care, Trip, Cochrane Library, and CINAHL databases were searched using the search terms pregnancy; stress; fetus; blood; Doppler; ultrasound. Studies were eligible for inclusion if prenatal stress was assessed with standardized measures, hemodynamics was measured with Doppler ultrasound, and methods were adequately described. A specifically designed data extraction form was used. The methodological quality of included studies was assessed using well-accepted quality-appraisal guidelines.

Results: Of 2,532 studies reviewed, 12 met the criteria for inclusion. Six reported that prenatal stress significantly affects maternal or fetal hemodynamics; six found no significant association between maternal stress and circulation. Significant relationships between prenatal stress and uterine artery RI and PI, umbilical artery RI, PI, and S/D ratio, fetal MCA PI, cerebroplacental ratio, and umbilical vein volume blood flow were found.

Conclusions: To date, there is limited evidence that prenatal stress is associated with changes in circulation. More carefully designed studies with larger sample sizes, repeated assessments across gestation, tighter control for confounding factors, and measures of pregnancy-specific stress will clarify this relationship.

Keywords: Blood flow, Doppler ultrasound, fetal well-being, pregnancy, psychological stress

Introduction

Pregnancy can be a stressful time for many women, particularly in the context of identified medical risks such as preeclampsia, intrauterine growth restriction, and previous preterm birth or miscarriage. Prenatal stress is psychological distress experienced by a woman during pregnancy. It can be influenced by many factors, including life events, ethnicity, social support, income level, educational background, resilience, attitudes towards pregnancy, and partner relationship quality (Gurung et al., 2005). Prenatal stress has been associated with stillbirth (Wisborg et al., 2008), preterm birth (Dole et al., 2003; Rondo et al., 2003; Sandman et al., 2006; Wadhwa et al., 2004), lower fetal weight (Diego et al., 2006; Henrichs et al., 2010; Kivlighan et al., 2008; Rondo et al., 2003; Wadhwa et al., 2004; Wright et al., 2010), delayed fetal neurodevelopment (Kinsella & Monk, 2009), altered innate and adaptive immune responses in offspring (Wright et al., 2010), altered hippocampal development (Qiu et al., 2013), "difficult" infant temperament (Austin et al., 2005; Davis et al., 2004, 2007, 2011; Gutteling et al., 2005), reduced cognitive development (Brouwers et al., 2001; Davis & Sandman, 2010; Huizink et al., 2002, 2003; King & Laplante, 2005; Laplante et al., 2004; O'Connor et al., 2003), behavioral reactivity (Davis et al., 2004, 2005, 2007), emotional and behavioral problems that persist into adolescence (van den Bergh et al., 2005, 2008), and lower academic achievement in school (Niederhofer & Reiter, 2004). However, not all studies report negative effects of prenatal stress on fetal and infant development (DiPietro et al., 2005). Other studies have found no adverse effects on birth weight, gestational age at delivery, or obstetric complications (Andersson et al., 2004; Littleton et al., 2007; Perkin et al., 1993).

Pregnancy-specific stress, an even more recent area of research, is a constellation of fears and concerns related to pregnancy itself, and can include worries about the health of the fetus, diet, weight gain, appearance, labor, and delivery (Alderdice & Lynn, 2011; Huizink et al.,

2004). Research into pregnancy-specific stress suggests that it may be a more sensitive predictor of pregnancy outcomes than general prenatal stress (Sandman et al., 2012; Wadhwa et al., 2011). Some studies indicate that measures of pregnancy-specific stress are more sensitive than measures of general prenatal stress in predicting developmental outcomes, including fetal behaviour (DiPietro et al., 2002), infant cognitive and motor development (Davis & Sandman, 2010; DiPietro et al., 2006; Huizink et al., 2003), and infant emotional regulation (DiPietro et al., 2006). Pregnancy-specific stress has been associated with shorter gestation (Roesch et al., 2004) and preterm birth (Dole et al., 2003; Kramer et al., 2009), delayed neurodevelopment (Davis & Sandman, 2010; Huizink et al., 2003), and shorter newborn leukocyte telomere length, a predictor of age-related diseases such as hypertension and Type 2 diabetes (Entringer et al., 2013). Pregnancy-specific stress has also been linked to alterations in brain structure and executive control deficits in childhood (Buss et al., 2010, 2011).

Potential interactions between prenatal or pregnancy-specific stress and blood flow in pregnancy remain relatively unexplored. Significant hemodynamic changes transpire in pregnancy in order to meet the needs of the developing fetus (Brunton et al., 2008; Duvekot & Peeters, 1994; Japundzic-Zigon, 2013). Doppler ultrasound offers a non-invasive method of measuring placental blood flow (Harville et al., 2008), and can be used to gather information about maternal and fetal circulations by insonating the uterine artery (UtA), umbilical artery (UA), fetal middle cerebral artery (MCA), and fetal venous circulation (Kochenour, 1993). Resistance to blood flow is increased in the UtA and UA when poor placentation occurs (Adamson et al., 1989), leading to higher velocimetry indices measured by the systolic/diastolic ratio (S/D), the pulsatility index (PI), and the resistance index (RI).

Increased resistance in the UtA has been linked to preeclampsia, fetal growth restriction (Hollis et al., 2003), and other adverse pregnancy outcomes (Aardema et al., 2004), while

increased resistance in the UA has been linked to fetal growth restriction, fetal distress, and long-term neurodevelopmental outcomes (Bartha et al., 1998). Abnormal blood flow in the fetal MCA is an indicator of fetal cardiovascular distress, hypoxia, or anemia. Lower resistance in the fetal MCA can indicate fetal "head-sparing," or blood redistribution in favor of fetal brain circulation. This is generally a response to hypoxia and acidosis, and is associated with intrauterine growth restriction (Johnson et al., 2001). The cerebroplacental ratio (CPR) is the ratio of MCA PI to UA PI, and has been proposed as a more sensitive predictor of adverse perinatal outcomes in fetal growth restriction than either umbilical artery or MCA values alone (Arias, 1994; Bahado-Singh et al., 1999; Gramellini et al., 1992; Odibo et al., 2005).

Although these Doppler waveform analysis parameters—UtA and UA RI, PI, and S/D ratio; fetal MCA; CPR; and umbilical vein blood flow—have been linked with adverse obstetric and neonatal outcomes, few studies have assessed their potential relationship with prenatal stress, and these studies have not been systematically reviewed. There is an obvious need to examine potential causes of abnormal maternal and fetal hemodynamics such as prenatal and pregnancy-specific stress. This systematic review was conducted in order to assess the quality of the available evidence of a relationship between prenatal stress and abnormal maternal or fetal hemodynamics as measured by Doppler waveform analysis.

Methods

Search Strategy

The search strategy for the included studies is outlined in Figure 1. We conducted a systematic literature search to identify studies from database inception through to 9 August 2015. The search strategy involved searching electronic databases and inspecting bibliographies of retrieved articles for any studies overlooked during database searching. We

searched the PubMed/Medline, EMBASE, PsycINFO, Maternity and Infant Care, Cochrane Library, Trip, and CINAHL databases. The following MeSH and text search terms were used: pregnancy; stress; blood; fetus; Doppler; ultrasound. An example electronic search strategy can be found in Appendix 1.

Selection of Eligible Studies

Studies were eligible for inclusion if they measured RI, PI, and/or S/D ratio in the UtA or UA, and/or fetal MCA, and/or the CPR, and/or umbilical vein blood flow using Doppler ultrasound in pregnant women, and measured maternal prenatal stress using at least one standardized measure of stress during pregnancy. Studies were determined to be ineligible if Doppler ultrasound measures were not conducted, study participants were not human, maternal prenatal stress was not assessed, or study methods were inadequately described. Given the relative scarcity of studies measuring the relationship between prenatal stress and Doppler ultrasound parameters, no additional limitations on study design or participant characteristics were included in the eligibility or ineligibility criteria.

Data Extraction and Synthesis

Data were retrieved using a specifically designed data-extraction form that included the following study details: authors, year of publication, location of study, gestational age at assessment, exclusion criteria, measure(s) used, results, and limitations. Available summary results were tabulated. A descriptive methodology was chosen, and the results are presented as a narrative synthesis of the existing literature related to the relationship between prenatal maternal stress and hemodynamics. These results are summarized in Table 2.

Quality Assessment

A well-accepted outline for assessing the quality of evidence relating to prognostics and health outcomes was utilized (Hayden et al., 2006). The outline evaluates six areas of potential bias: study participation, study attrition, prognostic factor measurement, outcome measurement, confounding factor analysis, and data analysis. The quality assessment outline can be found in Appendix 2. One author (TL) assessed the quality of the included papers and reviewed these decisions with the rest of the team. Studies were assigned a quality designation of + (yes: this aspect of potential bias is addressed), - (no: this aspect of potential bias is not addressed), ~ (partly: this aspect of potential bias is partly addressed), or U (unsure: it cannot be determined from the paper whether this aspect of potential bias is addressed) for each aspect of the six described domains of potential bias. Studies were not excluded on the basis of this quality assessment, as the purpose of this systematic review is to assess and describe the quality of all evidence currently available regarding the potential relationship between maternal prenatal stress and maternal-fetal hemodynamics as measured by Doppler ultrasound. Papers were not assigned a numerical score according to their assessed quality, and were given equal weight in the narrative presentation of their findings.

Results

Included Studies

The initial database search returned 2,532 studies. After an initial review of titles, 2,401 articles were excluded. Abstracts of the remaining 131 studies were then reviewed, and 119 studies were excluded according to the eligibility and ineligibility criteria. A total of 12 studies that assessed the interaction between human prenatal maternal stress and hemodynamics as measured by Doppler waveform analysis were identified and are summarized in Table 2. Full-text analysis of these studies was then conducted. Among these 12 studies, all were prospective cohort studies. All studies were conducted within

industrialized nations: USA (3), Norway (2), South Africa (2), the United Kingdom (2), and one each in Italy, Sweden, and Turkey. A total of 1,852 women were included in these twelve studies and a summary of their demographic information, substance use, and psychiatric diagnoses where reported can be found in Table 1. Brief descriptions of the ten standardized measures of stress used in the included studies can be found in Appendix 3.

Seven of the studies assessed healthy, medically low-risk pregnant women (Helbig et al., 2013; Kent et al., 2002; Mendelson et al., 2011; Roos et al., 2015; Sjostrom et al., 1997; Teixeira et al., 1999; Vythilingum et al., 2010), two assessed medically high-risk pregnant women (Caliskan et al., 2009; Helbig et al., 2011), and Harville et al. (2008) included both high- and low-risk participants. Two studies specifically assessed pregnant women with existing psychiatric diagnoses (Maina et al., 2008; Monk et al., 2012). The included studies had several limitations, including small sample sizes and significant variation in study design, study populations, measures used, gestational ages at assessment, and exclusion criteria. As meta-analysis was therefore not possible, the results are described in detail below, organized according to blood vessel, and summarized in Table 2.

Doppler parameters are reported in the included studies and therefore in this review as increased, decreased, or unaffected relative to stress measure scores rather than as clinically "normal" or "abnormal." While this may appear to limit immediate clinical utility of the studies' findings, it enables the elucidation of more subtle interactions between maternal mental health and fetal well-being. These studies explore the complex impact of maternal mental health on fetal development, and are therefore a valuable addition to research into fetal programming and the fetal origins of adult disease (Barker, 1998; Barker et al., 2002; Calkins & Devaskar, 2011; Entringer et al., 2010; Galjaard et al., 2013; Lombardo et al., 2012; Ross & Beall, 2008; Sandman et al., 2012).

Quality Assessment of Included Studies

Our assessment of the quality of studies included in this review, using the guidelines for assessment of prognostic studies (Hayden et al., 2006) provided in Appendix 2, is summarized in Table 3. Only one study adequately described the source population for key characteristics (Roos et al., 2015). One study (Caliskan et al., 2009) failed to provide exclusion criteria, and two studies failed to describe the study sample for key characteristics (Kent et al., 2002; Teixeira et al., 1999). Six studies (Caliskan et al., 2009; Helbig et al., 2011; Helbig et al., 2013; Kent et al., 2002; Teixeira et al., 1999; Vythilingum et al., 2010) were cross-sectional, with participants assessed at varying gestational ages, which can make it more difficult to assess acute versus chronic stress as well as changes in blood flow over time. All but one (Harville et al., 2008) study had small sample sizes, which can make it difficult to detect minor effects and does not allow conclusions about clinical significance. Five studies explicitly excluded participants on the basis of a pre-existing psychiatric diagnosis (Helbig et al., 2011; Helbig et al., 2013; Maina et al., 2008; Mendelson et al., 2011; Monk et al., 2012), and seven did not (Caliskan et al., 2009; Harville et al., 2008; Kent et al., 2002; Roos et al., 2015; Sjostrom et al., 1997; Teixeira et al., 1999; Vythilingum et al., 2010). Among the studies that did exclude according to psychiatric illness, specific exclusion criteria differed. Failure to report pre-existing psychiatric conditions in a study sample can make it difficult to generalize results to the non-psychiatric pregnant population.

None of the included studies that lost participants to follow-up adequately described study attrition. Although three studies (Helbig et al., 2013; Maina et al., 2008; Sjostrom et al., 1997) listed reasons why participants were lost to follow-up, none adequately described or compared key characteristics in participants who completed the study and those who did not. Attempts to collect information on participants who dropped out of the study were not described in any study. Prognostic factors and outcome measurement were adequately

described in all included studies. Standardized outcome measures decrease measurement bias and make comparability across studies less problematic but increase the risk of subjective response bias, and the choice of stress measures varied considerably. Only three studies (Helbig et al., 2011; Helbig et al., 2013; Mendelson et al., 2011) addressed pregnancy-specific stress. Four studies (Harville et al., 2008; Maina et al., 2008; Monk et al., 2012; Sjostrom et al., 1997) included a clinical interview to assess maternal psychological state, while eight (Caliskan et al., 2009; Helbig et al., 2011; Helbig et al., 2013; Kent et al., 2002; Mendelson et al., 2011; Roos et al., 2015; Teixeira et al., 1999; Vythilingum et al., 2010) relied on self-report measures. Adjustment for potentially confounding factors was only adequate in one study (Monk et al., 2012). Data analysis was adequately described in seven of the included studies (Caliskan et al., 2009; Harville et al., 2008; Helbig et al., 2011; Helbig et al., 2013; Roos et al., 2015; Sjostrom et al., 1997; Vythilingum et al., 2010).

Uterine Artery

Five studies examined the relationship between prenatal stress and uterine artery RI (Kent et al., 2002; Maina et al., 2008; Mendelson et al., 2011; Monk et al., 2012; Teixeira et al., 1999); one found significant results. Teixeira et al. (1999) found a significant association between state and trait anxiety scores and both mean and maximum RI (state/mean: $r_s = 0.28$, $p < 0.005$; state/maximum: $r_s = 0.31$, $p < 0.002$; trait/mean: $r_s = 0.28$, $p < 0.005$; trait/maximum: $r_s = 0.21$, $p < 0.03$). The best predictors of mean RI were state anxiety scores ($p < 0.001$) and maternal heart rate ($p < 0.02$), while the best predictor of maximum RI or notching was state anxiety score ($p < 0.01$).

Five studies examined the relationship between prenatal stress and uterine artery PI (Harville et al., 2008; Helbig et al., 2011; Helbig et al., 2013; Roos et al., 2015; Vythilingum et al., 2010); two found significant results. Vythilingum et al. (2010) found small positive

correlations between trait anxiety and uterine artery PI; however, these were not significant after adjustment for alcohol or nicotine ($F = 0.285$, $p = 0.597$). At 32-33 weeks' gestation, women scoring above the clinical cut-off on the Kessler Psychological Distress Scale (K-10) had higher uterine artery PI than those in the normal range of psychological distress ($F = 10.623$, $p = 0.002$), and this was significant after adjusting for alcohol and nicotine use or nicotine dependence. Roos et al. (2015) found that higher trait anxiety was a significant predictor of increased uterine artery pulsatility index in the first [$F(1,33) = 5.62$, $p = 0.024$; $R^2 = 0.15$, $b = 0.38$] and second trimesters [$F(1,106) = 5.43$, $p = 0.022$, $R^2 = 0.05$, $b = 0.22$]. Although Helbig et al. (2011) found no significant differences in UtA PI between women with and without recent diagnosis of fetal anomaly, the fetal anomaly group scored significantly higher ($p < 0.001$) than the healthy fetus group on all distress measures except the Somatisation subscale of the General Health Questionnaire (GHQ).

Umbilical Artery

Six studies examined the relationship between prenatal stress and umbilical artery RI (Caliskan et al., 2009; Harville et al., 2008; Helbig et al., 2011; Maina et al., 2008; Mendelson et al., 2011; Monk et al., 2012); one found significant results. Comparing women who were undergoing amniocentesis and those who were receiving routine ultrasonography, Caliskan et al. (2009) found that participant state anxiety scores were significantly higher in the amniocentesis group (48.9 ± 11.8) compared to the control group (33.5 ± 6.5, $p < 0.001$), and that umbilical artery RI was significantly higher in the amniocentesis group ($p < 0.05$).

Three studies examined the relationship between prenatal stress and umbilical artery PI (Helbig et al., 2013; Sjostrom et al., 1997; Vythilingum et al., 2010); two found significant results. Sjostrom et al. (1997) found that women with high trait anxiety scores had significantly higher umbilical artery PI values ($X^2 = 10.51$, $p = 0.0056$). Helbig et al. found

that the Intrusion subscale of the Impact of Event Scale-22 was negatively correlated with UA PI in the group of participants who had been diagnosed with a fetal anomaly (r_s = 0.23, p = 0.043). Women who reported a clinically important reaction to the anomaly diagnosis had a lower UA PI than those who reported a minor or moderate reaction (mean difference: 0.11, 95% CI: 0.00-0.22, p = 0.043), and the continuous Intrusion variable explained 13% of the variance in UA PI in multiple linear regression analyses (β= -0.006, p = 0.025). The authors comment that finding reduced resistance in the umbilical artery following a severe stressor is unexpected, and that the results should be interpreted with caution (Helbig et al., 2011).

Only one study reported the relationship between prenatal stress and umbilical artery S/D ratio in 120 women receiving either amniocentesis or routine early second trimester ultrasonographic screening. This study found that the S/D ratio was significantly higher in the amniocentesis group (p < 0.05). Time elapsed between being offered and receiving amniocentesis was the strongest predictor of the fetal umbilical artery S/D ratio measured prior to amniocentesis in the amniocentesis group (β = 0.66, p < 0.001), and maternal state anxiety score was the main predictor of fetal umbilical artery S/D ratio measured prior to amniocentesis or ultrasonography in both groups (β = 1.44, p = 0.02) (Caliskan et al., 2009).

Fetal Middle Cerebral Artery and Cerebroplacental Ratio

Three studies examined the relationship between prenatal stress and blood flow in the fetal middle cerebral artery (MCA) (Roos et al., 2015; Sjostrom et al., 1997; Vythilingum et al., 2010); two found significant results. Sjostrom et al. found that women with higher trait anxiety scores had lower MCA PI values (X^2= 7.83, p = 0.019) and cerebroplacental ratios (X^2= 18.67, p < 0.0001), reflecting a distributional change in blood flow in favor of fetal cerebral circulation, or "head-sparing," that remained robust even after adjustment for maternal height, weight, age, marital status, nicotine and alcohol use, and socioeconomic

factors. Likewise, women with higher state anxiety had lower cerebroplacental ratios (X^2= 6.96, p = 0.031). All PI values were within the normal range for gestational age. Roos et al. (2015) found a significant association between higher state anxiety and increased fetal blood flow in the MCA in the third trimester [F(1,104) = 4.29, p = 0.041, R^2 = 0.04].

Umbilical Vein Volume Blood Flow

Helbig et al. assessed 104 women using the Impact of Event Scale-22 to measure maternal emotional response to "the condition of the child," or pregnancy-specific stress. The study found that lower umbilical vein volume blood flow was significantly correlated with higher scores on the Intrusion subscale, which assesses intrusive and unbidden thoughts, emotions, dreams, and memories, after adjustment for maternal age (β= -0.302, p = 0.003). This relationship was strengthened by adjusting for both maternal age and UA PI (β= -0.325, p < 0.001). The authors posit that intrusive thoughts and emotional distress about the fetus and their association with reduced fetoplacental blood flow in the third trimester may be a link between maternal distress and reduced fetal growth (Helbig et al., 2013).

Discussion

Although prenatal stress is associated with adverse fetal and neonatal outcomes (Diego et al., 2006; Henrichs et al., 2010; Kivlighan et al., 2008; Qiu et al., 2013; Rondo et al., 2003; Sandman et al., 1997; Wadhwa et al., 1993, 2004; Wisborg et al., 2008; Wright et al., 2010), the biological mechanisms underlying this relationship remain unclear. The twelve studies included in this systematic review examine the relationship between prenatal stress and maternal and fetal hemodynamics as measured by Doppler ultrasound. Six of these indicate that prenatal stress significantly affects some aspect of maternal or fetal hemodynamics (Caliskan et al., 2009; Helbig et al., 2013; Roos et al., 2015; Sjostrom et al., 1997; Teixeira et al., 1999; Vythilingum et al., 2010), while the other six found no significant association

(Harville et al., 2008; Helbig et al., 2011; Kent et al., 2002; Maina et al., 2008; Mendelson et al., 2011; Monk et al., 2012). Significant relationships between prenatal stress and uterine artery RI (Teixeira et al., 1999) and PI (Roos et al., 2015; Vythilingum et al., 2010); umbilical artery RI (Caliskan et al., 2009), PI (Sjostrom et al., 1997), and S/D ratio (Caliskan et al., 2009); fetal MCA (Roos et al., 2015; Sjostrom et al., 1997); cerebroplacental ratio (Roos et al., 2015; Sjostrom et al., 1997); and umbilical vein volume (Helbig et al., 2013) blood flow were reported. These twelve studies do not provide conclusive evidence of a relationship between prenatal stress and maternal or fetal hemodynamics. However, their strengths and limitations can inform future research into the impact of maternal mental health on fetal well-being.

The most important barrier to furthering our understanding of the possible relationship between prenatal stress and maternal and fetal hemodynamics is the failure of these studies to repeatedly measure and report all Doppler parameters in every participant across gestation in the same clinic visits during which maternal mental health is assessed. There is evidence that the timing of stress can have different effects on pregnancy, birth, and early childhood development outcomes (Ellman et al., 2008; Glynn et al., 2008; Sandman et al., 2006; Scheyer & Urizar, 2015). Simultaneous, complete, repeated collection of Doppler waveform and prenatal stress data across gestation in future studies will help to clarify the complex and possibly time-dependent nature of these interactions.

Despite extensive research linking low socioeconomic status to adverse pregnancy and birth outcomes such as preeclampsia, intrauterine growth restriction, and preterm birth (Haelterman et al., 2003; Moser et al., 2003; Peacock et al., 1995; Raum et al., 2001; Silva et al., 2008, 2010), few studies included in this systematic review adequately attend to such factors. Harville et al. (2008) underscore their importance: UA RI was higher in younger women, those with less education, those who were single, and those who smoked, while UtA

PI was higher in women with preeclampsia, who were living alone, had high BMI, or who had gained the least weight during pregnancy. Importantly, these factors are also commonly associated with psychological stress. These findings are supported by a recent study of 7,033 pregnant women which found that women with lower educational levels, especially those who smoke, have higher UtA RI and UA PI (Bouthoorn et al., 2014). There is also growing evidence that ethnic disparities in birth outcomes may be at least partially explained by the experience of racism and race-related discrimination (Dole et al., 2003; Duncan et al., 2012; Giscombe et al., 2005; Hilmert et al., 2014; Lobel et al., 2008). None of the twelve studies measured perceived racism, and only Harville et al. reported adjusting for ethnicity.

A noteworthy strength of the study by Roos et al. (2015) is their decision to include the Multidimensional Scale of Perceived Social Support and the Connor-Davidson Resilience Scale, which measures the ability of the respondent to cope with stressful events in the preceding month. This group found that considering social support strengthened the already significant association between higher state anxiety and lower MCA PI in the third trimester. Lobel and colleagues offer thorough reviews of prenatal stress research and the importance of utilizing a multidimensional approach to analyzing stress in pregnancy (Lobel, 1994; Lobel et al., 2008). Increased inclusion of such scales and greater attention to socioeconomic status and substance use in future interdisciplinary studies will provide researchers, clinicians, and patients with a more holistic understanding of the impact of maternal mental health on fetal well-being.

Monk et al. (2012) moreover demonstrate the importance of accounting for the potential influences of psychiatric medication. This group studied the interactions of prescription drug use and Doppler indices, and found that chronic bupropion exposure was associated with higher UA ($r = 0.38$, $p = 0.002$), left UtA ($r = 0.26$, $p = 0.029$), and sum UtA ($r = 0.28$, $p = 0.022$) RI after excluding women with obstetric complications and those using nicotine

(Monk et al., 2012). Likewise, atypical antipsychotic use was associated with increased UA RI after excluding women using nicotine products ($r = 0.36$, $p = 0.0004$). Only three (Maina et al., 2008; Mendelson et al., 2011; Sjostrom et al., 1997) of the included studies excluded participants for psychiatric medication use, and no other study as closely examined its potentially confounding influence on Doppler indices. Failure to adjust for psychiatric medication during these studies can gravely impair the utility of their results.

In this review, we have evaluated the quality of the available evidence regarding the relationship between Doppler waveform parameters and prenatal stress. The findings of the twelve included studies are inconclusive, and should be considered preliminary. Due to their small sample sizes, cross-sectional study designs, inconsistent measurement of all Doppler parameters, heterogeneous use of stress measures, lack of adjustment for confounders, and failure to either explicitly exclude women with psychiatric diagnoses or who are taking psychiatric medication or explicitly include study groups with these characteristics, it is impossible to determine from the available evidence whether maternal prenatal stress is associated with hemodynamic changes during pregnancy. In light of the substantial literature demonstrating an association between maternal stress and adverse fetal outcomes, the potential relationship between maternal prenatal stress and maternal-fetal hemodynamics merits further investigation with more carefully designed studies.

Within the context of current perinatal stress research, which has established that high levels of stress during pregnancy pose risks to maternal and infant health (Buss et al., 2010, 2011, 2012; Davis et al., 2004, 2005, 2007, 2011; Davis & Sandman, 2010; Sandman et al., 2012), the relationship between prenatal stress and maternal and fetal hemodynamics merits a great deal of further investigation. Given the rapidly growing evidence linking pregnancy-specific stress with adverse fetal, infant, and childhood outcomes (Alderdice & Lynn, 2011; Buss et al., 2010, 2011; Davis & Sandman, 2010; DiPietro et al., 2002, 2006; Dole et al., 2003;

Huizink et al., 2003, 2004; Kramer et al., 2009; Roesch et al., 2004; Sandman et al., 2012; Wadhwa et al., 2011), and the fact that only three of the twelve studies included in this review measured pregnancy-specific stress (Helbig et al., 2011; Helbig et al., 2013; Mendelson et al., 2011), there is an obvious need to explore any potential connection between pregnancy-specific stress and maternal-fetal circulation during pregnancy. As evidence of the complex interactions between maternal mental health and adverse fetal and child outcomes continues to grow, there is an opportunity to consider increased allocation of resources to researching and reducing women's stress and stress-related behaviours such as substance use. More consideration of support and interventional strategies (Bailey, 2010; Campbell, 1998; McFarlane et al., 2000; Winn et al., 2003) which may ameliorate the relationship between prenatal stress and fetal well-being is also needed.

Conclusions

To our knowledge, this is the first systematic review of studies evaluating the relationship between prenatal stress and maternal-fetal blood flow in pregnancy. Evidence of an association between prenatal stress and changes in maternal and fetal circulation during pregnancy remains inconclusive, due in part to the methodological limitations of available studies. More carefully designed studies with larger sample sizes, repeated assessments across gestation, tighter control for confounding factors such as psychiatric illness and medication use, and greater attention to pregnancy-specific stress will clarify this relationship and may determine whether prenatal stress is involved in the biological mechanisms underlying adverse changes in blood flow during pregnancy.

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Appendix 1: Example Search Strategy

("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]) AND ("Stress"[Journal] OR "stress"[All Fields]) AND ("blood"[Subheading] OR "blood"[All Fields] OR "blood"[MeSH Terms]) AND ("foetus"[All Fields] OR "fetus"[MeSH Terms] OR "fetus"[All Fields]) AND Doppler[All Fields] AND ("ultrasonography"[Subheading] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields])

Appendix 2: Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework of Potential Biases(Hayden et al., 2006)

Potential Bias	Items to be Considered for Assessment
Study Participation: the study sample represents the population of interest on key characteristics sufficient to limit potential bias to the results (yes, partly, no, or unsure)	1. The source population or population of interest is adequately described for key characteristics. 2. The sampling frame and recruitment are adequately described, possibly including methods to identify the sample (number and type used, e.g., referral patterns in health care), period of recruitment, and place of recruitment (setting and geographic location). 3. Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero-time" description. 4. There is adequate participation in the study by eligible individuals. 5. The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics.
Study Attrition: loss to follow-up (from sample to study population) is not associated with key characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias (yes, partly, no, or unsure)	1. Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate. 2. Attempts to collect information on participants who dropped out of the study are described. 3. Reasons for loss to follow-up are provided. 4. Participants lost to follow-up are adequately described for key characteristics. 5. There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.
Prognostic Factor Measurement: the prognostic factor of interest is adequately measured in study participants to sufficiently limit bias (yes, partly, no, or unsure)	1. A clear definition or description of the prognostic factor measured is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement). 2. Continuous variables are reported or appropriate (i.e., not data-dependent) cut-points are used. 3. An adequate proportion of the study sample has complete data for prognostic factors. The method and setting of measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing prognostic factor data.
Outcome Measurement: the outcome of interest is adequately measured in study participants to sufficiently limit potential bias (yes, partly, no, or unsure)	1. A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct. 2. The outcome measure and method used are adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, and may include characteristics, such as blind measurement and confirmation of outcome with valid and reliable test). 3. The method and setting of measurement are the same for all study participants.
Confounding Measurement and Account: important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (yes, partly, no, or unsure)	1. All important confounders including treatments are measured. 2. Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures). 3. Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, and may include characteristics such as blind measurement and limited reliance on recall). 4. The method and setting of confounding measurement are the same for all study participants. 5. Appropriate methods are used if imputation is used for missing confounder data. 6. Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups). 7. Important confounders are accounted for in the analysis (i.e., appropriate adjustment).

Analysis: the statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (yes, partly, no, or unsure)	1. There is sufficient presentation of data to assess the adequacy of the analysis. 2. The strategy for model-building (i.e., inclusion of variables) is appropriate and is based on a conceptual framework or model. 3. The selected model is adequate for the design of the study. 4. There is no selective reporting of results.

Appendix 3: Standardized Stress Measures

1. Cohen Perceived Stress Scale (PSS-10):(Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988; DiPietro, Costigan, & Sipsma, 2008) a 10-item self-report measure that assesses the extent to which life is experienced by the participant as unpredictable, uncontrollable, and demanding. Participants rate their distress during the last month, and higher scores indicate higher perceived stress. The PSS-10 was used in 3 of the included studies.(Harville et al., 2008; Roos et al., 2015; Vythilingum et al., 2010)
2. General Health Questionnaire (GHQ):(Goldberg, 1978) a measure of the prevalence of mental disorders in a given population, or of psychological distress and well-being in clinical and non-clinical populations. The 28-item version has 4 subscales rated on a Likert scale of 0-3, with subscale scores ranging from 0-21. Scores of ≥6 are considered clinically relevant. The 4 subscales are Somatization, Social Dysfunction, Anxiety and Insomnia, and Depression. The GHQ was used in 2 of the included studies.(Helbig et al., 2011; Helbig et al., 2013)
3. Hamilton Rating Scales of Anxiety (HAM-A):(Hamilton, 1959) a 17-item scale that measures symptoms of anxiety, including items related to mood, tension, concentration, insomnia, memory, fears, and somatic symptoms. The HAM-A was used in 2 of the included studies.(Maina et al., 2008; Monk et al., 2012)
4. Hospital Anxiety and Depression Scale (HAD):(Aylard, Gooding, McKenna, & Snaith, 1987; Wilkinson & Barczak, 1988; Zigmond & Snaith, 1983) a self-rating scale designed for use in hospital and community settings with a threshold score for definite cases of anxiety (≥11 on a 0-28 scale). The HAD was used in 1 of the included studies.(Kent et al., 2002)
5. Impact of Event Scale (IES):(Horowitz, Wilner, & Alvarez, 1979) a 22-item scale that measures subjective psychological distress after a specific traumatic event using three subscales—Intrusion (7 items, 0-35 range) dealing with unbidden thoughts, emotions, and memories; Avoidance (7 items, 0-35 range) dealing with emotional numbness and avoiding stimuli or thoughts related to the event; and Arousal (8 items, 0-40 range) dealing with symptoms of psycho-physiological activation such as hypervigilance, irritability, and heightened startle response. Subscale scores ≥20 indicate clinical relevance. The IES was used in 2 of the included studies.(Helbig et al., 2011; Helbig et al., 2013)
6. John Henryism:(James, 1994) a 12-item scale that assesses coping in an active way, overcoming obstacles, and “making one’s own way in the world”. John Henryism was used in 1 of the included studies.(Harville et al., 2008)
7. Kessler-10 (K-10):(Kessler et al., 2002; Kessler, 2003; Spies et al., 2009) a 10-item self-report measure that assesses general distress; participants rate statements about their feelings during the last month on a 5-point Likert scale. A cut-off score of 20 is considered clinically significant. The K-10 was used in 2 of the included studies.(Roos et al., 2015; Vythilingum et al., 2010)
8. Pregnancy Experiences Scale (PES-Brief):(DiPietro, Ghera, Costigan, & Hawkins, 2004) the PES-Brief includes the 10 most frequently endorsed hassles and uplifts from the full PES; each item is rated on a 0-4 Likert scale and then averaged—higher values reflect higher perceived intensity of negative or positive feelings about the pregnancy. The PES-Brief was used in 1 of the included studies.(Mendelson et al., 2011)

9. Sarason's Life Experiences Survey (LES):(Sarason, Johnson, & Siegel, 1978) a 39-item scale designed to measure life events and their perceived impact. The LES was used in 1 of the included studies.(Harville et al., 2008)
10. Spielberger's State-Trait Anxiety Inventory (STAI):(DiPietro et al., 2008; Spielberger, 1983) a widely used 40-item self-report inventory of the current (state, S) and inherent (trait, T) level of anxiety. Twenty items are dedicated to evaluating state anxiety; the other 20 evaluate trait anxiety. The S score indicates how anxious the patient is feeling in response to a defined situation, while the T score indicates how anxious the individual generally feels. Each item is scored 1-4, and total scores range between 20-80. The STAI was used in 7 of the included studies.(Caliskan et al., 2009; Harville et al., 2008; Mendelson et al., 2011; Roos et al., 2015; Sjostrom et al., 1997; Teixeira et al., 1999; Vythilingum et al., 2010)

Table 1: Demographic Characteristics of Included Women (n= 1852)

	Reported n	n (%)
Employed	1319	880 (66.7%)
Marital Status		
Single	1423	391 (27.5%)
Married	1444	938 (64.9%)
Living with a Partner	321	59 (18.4%)
Separated, divorced, or widowed	1020	41 (4.0%)
Smokers	1780	232 (13.0%)
Drinkers	179	27 (15.1%)
Nulliparous	1748	971 (55.6%)
Ethnicity		
White	1080	788 (72.9%)
Black	1080	203 (18.8%)
Hispanic	101	2 (1.9%)
Mixed	247	233 (94.3%)
Other	1127	91 (8.1%)
Psychiatric Disorders		
Major Depressive Disorder	288	71 (24.7%)
Bipolar Disorder	285	32 (11.2%)
Anxiety Disorder(s)	101	60 (59.4%)
Psychosis	205	0
No Psychiatric Disorder	201	107 (53.2%)

Table 2: Included Studies

Citation	Study Group(s)	GA at Assessment	Stress Measure(s)	Doppler Parameter(s)	Main Findings	Results				
Caliskan 2009	60 singleton pregnant women having amniocentesis, 60 having routine ultrasound	16-20 w	STAI	UA PI, RI, and S/D ratio, right and left UtA PI, RI, and S/D ratio	Maternal state anxiety, UA RI, and UA S/D ratio were significantly higher in the amniocentesis group.	STAI: *mean (SD)*	Amniocentesis		Routine Ultrasound	
						State anxiety	48.9 (11.8)		33.5 (6.5) ***	
						Trait anxiety	46.4 (7.3)		45 (5.1)	
Harville 2008	872 women	STAI 16w; UtA 17w; interview 19w; UtA, UA 26w; PSS, STAI 27w	2 telephone interviews, PSS, STAI	UtA PI, S/D ratio, and notching; UA RI, S/D ratio, and presence and direction of diastolic flow	Psychosocial stress was not consistently associated with higher placental resistance.		Association with UA RI, adjusted for GA and covariates			
						Psychosocial Measure	n	β	95% CI	p
						Negative Life Events, Interview 1	602			0.02
						1st Quartile		Ref.		
						2nd Quartile		-0.002	-0.014, 0.009	
						3rd Quartile		-0.013	-0.027, 0.002	
						4th Quartile		0.015	-0.001, 0.031	
						Negative Life Events, self-report 2	588			0.83
						1st Quartile		Ref.		
						2nd Quartile		-0.003	-0.015, 0.008	
						3rd Quartile		-0.001	-0.014, 0.012	
						4th Quartile		0.004	-0.012, 0.020	
						Total Life Events, Interview 1	603			0.14
						1st Quartile		Ref.		
						2nd Quartile		-0.001	-0.015, 0.013	
						3rd Quartile		-0.013	-0.028, 0.001	

						4th Quartile		0.000	-0.015, 0.016	
						Total Life Events, self-report 2	653			0.70
						1st Quartile		Ref.		
						2nd Quartile		-0.003	-0.015, 0.010	
						3rd Quartile		-0.006	-0.019, 0.008	
						4th Quartile		0.002	-0.012, 0.016	
						Perceived Stress, Interview 1	602			0.76
						1st Quartile		Ref.		
						2nd Quartile		0.000	-0.013, 0.013	
						3rd Quartile		0.000	-0.014, 0.013	
						4th Quartile		-0.007	-0.022, 0.008	
						Perceived Stress, Interview 2	614			0.09
						1st Quartile		Ref.		
						2nd Quartile		0.012	-0.001, 0.025	
						3rd Quartile		-0.002	-0.015, 0.011	
						4th Quartile		0.009	-0.005, 0.023	
						Anxiety, self-report 1	636			0.56
						1st Quartile		Ref.		
						2nd Quartile		-0.005	-0.010, 0.017	
						3rd Quartile		0.002	-0.009, 0.016	
						4th Quartile		0.005	-0.004, 0.022	
						Anxiety, self-report 2	614			0.60
						1st Quartile		Ref.		
						2nd Quartile		0.004	-0.010, 0.017	
						3rd Quartile		0.004	-0.009, 0.016	
						4th Quartile		0.009	-0.004, 0.022	
						Trait anxiety, self-report 1	640			1.00
						1st Quartile		Ref.		
						2nd Quartile		0.001	-0.012, 0.013	
						3rd Quartile		-0.001	-0.014, 0.012	
						4th Quartile		-0.001	-0.015, 0.012	
						John Henryism (active coping)	584			0.90
						1st Quartile		Ref.		
						2nd Quartile		0.002	-0.012, 0.015	
						3rd Quartile		0.005	-0.009, 0.018	
						4th Quartile		0.004	-0.009, 0.018	
							Association with UtA PI, adjusted for GA and covariates			

						Negative Life Events impact	647			0.40
						1st Quartile		Ref.		
						2nd Quartile		0.021	-0.028, 0.069	
						3rd Quartile		0.052	-0.040, 0.070	
						4th Quartile		0.014	-0.068, 0.057	
						All Life Events impact	667			0.74
						1st Quartile		Ref.		
						2nd Quartile		0.013	-0.035, 0.061	
						3rd Quartile		0.030	-0.029, 0.089	
						4th Quartile		-0.004	-0.071, 0.062	
						Perceived Stress	570			0.48
						1st Quartile		Ref.		
						2nd Quartile		0.024	-0.033, 0.082	
						3rd Quartile		0.027	-0.034, 0.088	
						4th Quartile		0.050	-0.019, 0.120	
						State Anxiety	652			0.23
						1st Quartile		Ref.		
						2nd Quartile		0.012	-0.042, 0.066	
						3rd Quartile		0.035	-0.018, 0.089	
						4th Quartile		0.043	-0.016, 0.102	
						Trait Anxiety	678			0.72
						1st Quartile		Ref.		
						2nd Quartile		0.049	-0.010, 0.108	
						3rd Quartile		0.025	-0.035, 0.085	
						4th Quartile		0.048	-0.015, 0.110	
						John Henryism (active coping)	563			0.91
						1st Quartile		Ref.		
						2nd Quartile		0.007	-0.058, 0.071	
						3rd Quartile		0.022	-0.044, 0.087	
						4th Quartile		0.015	-0.051, 0.080	
Helbig 2011	86 pregnant women with newly detected fetal	16-22 w	IES, GHQ-28	UtA and UA PI, notching, MHR	Although psychological distress was higher in women	*Mean (SD)*	Fetal Anomaly Group			Healthy Fetus Group (n= 98)
							Uterine Artery (n= 86)		Umbilical Artery (n= 76)	
						Impact of Event Scale				
						Intrusion	21.8 (8.9)***		21.8 (9.1)***	9.3 (6.3)
						Avoidance	10.4 (6.3)***		10.8 (6.3)***	2.1 (3.8)

	anomaly, 98 women with normal ultrasound				with a diagnosed fetal anomaly, psychological distress was not associated with circulatory resistance measures.	Arousal	14.5 (8.9) ***	14.0 (8.8)***	4.0 (4.7)
						General Health Questionnaire			
						Sum Likert score	26.5 (11.1)***	25.9 (10.9)***	19.6 (8.1)
						Sum case score	7.3 (5.7)***	7.1 (5.8)***	4.3 (4.2)
						Somatisation	7.2 (3.8)*	6.9 (3.6)	6.0 (3.5)
						Anxiety	8.4 (4.3)***	8.2 (4.3)***	5.5 (3.3)
						Social dysfunction	9.2 (2.7)***	9.2 (2.7)***	7.8 (2.4)
						Depression	1.7 (2.8)***	1.7 (2.8)***	0.3 (0.9)
						Circulatory Outcome Measures			
						UtA PI (median (IQR))	0.91 (0.73-1.13)		0.94 (0.77-1.13)
						UtA notching (n (%))	31 (36%)		40 (41%)
						MHR (bpm)	76.4± 10.7		75.2 (9.3)
						UA PI (median (IQR))		1.33 (1.17-1.47)	1.35 (1.25-1.48)
						FHR (bpm)		147.4 (7.2)	147.0 (7.7)
Helbig 2013	104 healthy pregnant women	30 w	GHQ-28, IES-22	UtA and UA RI and UVVBF normalized for FAC	Intrusive thoughts and emotional distress about the fetus were associated with reduced normalized umbilical	Associations between IES Intrusion and UVVBF, adjusted for maternal age and UA PI				
							B	95% CI	β	p
						Continuous distress measure				
						IES Intrusion	-0.045	-0.083, -0.007	-0.226	0.020
						Maternal age (years)	0.064	0.002, 0.126	0.196	0.044
						UA PI	-2.583	-4.123, -1.042	-0.318	0.001
						Dichotomous distress measure				
						IES Intrusion > mean	-0.879	-1.370, -0.382	-0.325	0.001
						Maternal age (years)	0.060	0.001, 0.120	0.186	0.047
						UA PI	-2.728	-4.220, -1.237	-0.335	<0.001

					vein volume blood flow. This association was strengthened following adjustment for UA PI.					
Kent 2002	96 primigravid women at routine 20w scan	20-22 w	HADS	UtA RI and notching	No association was found between anxiety scores and UtA RI or notching.		Doubtful or no anxiety	Definite anxiety	Diff/RR (95% CI)	
						Mean UtA RI (95% CI)	0.54 (0.51-0.55)	0.56 (0.52-0.61)	Diff: 0.026 (-0.01-0.07)	
						UtA notching (n (%))	10/77 (13.0%)	3/19 (15.8%)	RR: 1.22 (0.37-3.99)	
Maina 2008	20 mothers with psychiatric disorders, 20 exposed to stressful life events, 40 without stressor exposure	Psych assessment 18 w, ultrasound 20, 34±1 w	Structured interview, HAM-A	FHC, FAC, femur length, UtA, UA	There were no significant differences among the three groups on any of the ultrasound variables.	*n (%)*	Mothers with Psychiatric Disorders	Mothers Exposed to Serious Life Events	Healthy, Unstressed Mothers	
						FAC <10th				
						Abnormal	0	2 (10)	0	
						Normal	20 (100)	18 (90)	40 (100)	
						UtA (34±1w)				
						Abnormal	1 (5)	0 (0)	1 (2.5)	
						Normal	19 (95)	20 (100)	39 (97.5)	
						UA (34± 1 w)				
						Abnormal	0	0	0	
						Normal	20 (100)	20 (100)	40 (100)	

Mendelson 2011	107 women with healthy singleton pregnancies	5 visits spanning 24-38w	STAI, PES	UtA and UA RI	Psychological wellbeing was associated with decreased left UtA RI, and psychological distress was associated with lower right UtA RI. STAI, CES-D, WHO-5, and PES-Brief hassle scores were not correlated with UA or UtA RI at any visit.		Umbilical Artery RI			Right Uterine Artery RI			Left Uterine Artery RI		
						Fixed Effects	**Estimate**	**SE**	**t**	**Estimate**	**SE**	**t**	**Estimate**	**SE**	**t**
						Intercept	0.57	0.01	95.53****	0.45	0.01	49.08**	0.46	0.01	53.93****
						GA	-0.009	0.001	-15.08****	-0.005	0.001	-5.60****	-0.002	0.001	2.73*
						Parity	-0.002	0.01	-0.22	0.03	0.01	2.21*	0.02	0.01	2.28*
						Maternal Distress	-0.001	0.001	-0.58	-0.005	0.002	-2.35*	0.001	0.002	0.49
						Random Effects	**Estimate**	**SE**	**Z**	**Estimate**	**SE**	**Z**	**Estimate**	**SE**	**Z**
						Intercept Variance	0.001	0.000	3.84****	0.002	0.001	3.88****	0.002	0.000	4.05****
						Residual	0.002	0.000	12.93****	0.005	0.000	12.47****	0.005	0.000	12.66****
						Fixed Effects	**Estimate**	**SE**	**t**	**Estimate**	**SE**	**t**	**Estimate**	**SE**	**t**
						Intercept	0.57	0.01	95.62****	0.45	0.01	48.84****	0.46	0.01	54.60****
						GA	-0.009	0.001	-15.14****	-0.005	0.001	-5.58****	-0.002	0.001	2.79*
						Parity	-0.003	0.01	-0.39	0.03	0.01	2.25*	0.02	0.01	2.09
						Maternal	-0.003	0.002	-1.30	0.003	0.003	0.97	-0.006	0.003	-2.09*

						Well-Being									
						Random Effects	**Estimate**	**SE**	**Z**	**Estimate**	**SE**	**Z**	**Estimate**	**SE**	**Z**
						Intercept Variance	0.001	0.000	3.884***	0.002	0.001	3.888***	0.002	0.000	4.055***
						Residual	0.002	0.000	12.93***	0.005	0.000	12.47***	0.005	0.000	12.66***
Monk 2012	101 pregnant women with lifetime histories of mental illness	Every 4-6w from before 16 to 25w gestation, Doppler at 25w	Structured clinical interview, structured Interview for HAM-A	UA	There were no significant associations between acute, proximal, chronic measures of maternal anxiety and blood flow.	Numerical results for associations between maternal anxiety and blood flow are not presented in the paper.									
Roos 2015	148 women with healthy singleton pregnancies	13-14 w, 22-23 w, 32-33 w	K-10, STAI, PSS	UtA/UA RI/PI at T1/2/3, fetal MCA PI at T2/3	Higher trait anxiety was associated with increased UtA PI at		F	df	p	R^2	b				
						Higher trait anxiety and higher UtA PI									
						Trimester 1	5.62	1, 33	.024	0.15	0.38				
						Trimester 2	5.43	1, 106	.022	0.05	0.22				
						Trimester 3	Not reported	Not reported	0.87	Not reported	Not reported				

					trimester 1 and 2 but did not reach significance at trimester 3. Higher state anxiety was significantly associated with lower MCA PI at trimester 3.	Higher state anxiety and lower MCA PI					
						Trimester 1	Not reported	Not reported	Not reported	Not reported	Not reported
						Trimester 2	Not reported	Not reported	Not reported	Not reported	Not reported
						Trimester 3	4.29	1, 104	0.041	0.04	Not reported
						Trimester 3 adjusted for social support	4.73	1, 103	0.011	0.08	-0.29
Sjostrom 1997	37 healthy primigravid women	Psychological assessment at 12, 25, 36 w, postpartum within 6 m of delivery. Doppler at 36 w	Semi-structured interview and STAI on all four visits	UA PI, MCA PI	High trait anxiety was associated with significantly higher UA PI, significantly lower MCA PI, and significantly lower CPR.	STAI	State Anxiety			Trait Anxiety		
						UA PI	Low	Medium	High	Low	Medium	High
						Mean	0.82	0.97	0.88	0.79	0.97	0.93
						SD	0.10	0.14	0.19	0.10	0.17	0.15
						Median	0.79	0.98	0.87	0.79	0.95	0.89
							Low v. high, p=0.41			Low v. high, p=0.0056		
							Low v. med, p=0.01			Low v. med, p=0.0084		
							Med v. high, p=0.13			Med v. high, p=0.43		
						MCA PI	Low	Medium	High	Low	Medium	High
						Mean	1.45	1.33	1.40	1.52	1.41	1.26
						SD	0.33	0.21	0.31	0.22	0.38	0.18

						Median	1.4	1.3	1.3	1.52	1.37	1.22
							Low v. high, p=0.46			Low v. high, p=0.0029		
							Low v. med, p=0.34			Low v. med, p=0.38		
							Med v. high, p=0.80			Med v. high, p=0.22		
						CPR	Low	Medium	High	Low	Medium	High
						Mean	1.83	1.41	1.60	1.94	1.47	1.3
						SD	0.43	0.36	0.26	0.24	0.33	0.29
						Median	1.84	1.4	1.65	1.92	1.51	1.36
							Low v. high, p=0.08			Low v. high, p=0.0002		
							Low v. med, p=0.02			Low v. med, p=0.0004		
							Med v. high, p=0.19			Med v. high, p=0.51		
Teixeira 1999	100 pregnant women with singleton pregnancies	Mean 28-32 w	Questionnaire about emotional problems, major life events, STAI	UtA and UA RI, fetal MCA	State and trait anxiety were both significantly associated with UtA RI. A higher proportion of women with high state anxiety had notches in the UtA wavefor		Low Anxiety			High Anxiety		
						Mean (95% CI)						
						Mean RI	0.47 (0.45-0.49)			0.58 (0.50-0.67)****		
						Maximum RI	0.51 (0.49-0.54)			0.63 (0.56-0.71)***		
						N (%)						
						Mean RI ≥ 0.68	3 (4)			4 (27)**		
						With notching	4 (5)			4 (27)*		

					m pattern.			
Vythilingum 2010	Healthy pregnant women with singleton pregnancies	T1: 13-14 w, T2: 21-22 w, T3: 32-33 w	STAI, PSS, K-10	UtA, UA, MCA PI	There were no significant associations between measures of distress and anxiety and UA PI or MCA PI at any time point. In the third trimester (T3), women with K10 scores >20 had significantly higher UtA PI than those with scores below 20.	Associations with UtA PI in the Third Trimester, adjusted for confounders		
							F	p
						K-10	10.623	0.002
						PSS	0.134	0.716
						State anxiety	0.001	0.978
						Trait anxiety	0.285	0.597

*: p<0.05; **: p<0.01; ***: p<0.001; ****: p<0.0001. BPM: beats per minute; CI: confidence interval; CRH: corticotropin-releasing hormone; HADS: Hospital Anxiety and Depression Scale; f: female; FAC: fetal abdominal circumference; FHC: fetal head circumference; FHR: fetal heart rate; GA: gestational age; n: number of subjects/observations; GHQ: General Health Questionnaire; HAM-A: Hamilton Rating Score of Anxiety; HE-g: healthy mothers not exposed to life stressors; IES: Impact of Event Scale; IQR: interquartile range; K-10: Kessler 10; KW: Kruskal-Wallis test; LE-g: mothers exposed to stressful life events; MCA: middle cerebral artery; MHR: maternal heart rate; m: months; NLE: negative life events; NS: not significant; PES: Pregnancy Experiences Scale; PI: pulsatility index; PSS: Perceived Stress Scale; PSY-g: mothers with psychiatric disorders; RI: resistance index; RR: risk ratio; SAQ: self-administered questionnaire; S/D: systolic/diastolic; SGA: small for gestational age; STAI: State-Trait Anxiety Inventory; T1, 2, 3: trimester 1, 2, 3; TLE: total life events; UA: umbilical artery; UtA: uterine artery; UVVBF: umbilical vein volume blood flow; w: weeks.

Table 3: Quality Assessment of Included Studies

	Caliskan 2009	Harville 2008	Helbig 2011	Helbig 2013	Kent 2002	Maina 2008	Mendelson 2011	Monk 2012	Roos 2015	Sjostrom 1997	Teixeira 1999	Vythilingum 2010
Study Participation												
The source population or population of interest is adequately described for key characteristics.	-	-	-	-	-	-	-	-	+	-	-	-
The sampling frame and recruitment are adequately described, possibly including methods to identify the sample, period of recruitment, and place of recruitment.	~	+	~	~	+	+	~	-	~	~	~	~
Inclusion and exclusion criteria are adequately described.	-	+	+	+	+	+	+	+	+	+	+	+
There is adequate participation in the study by eligible individuals.	+	+	+	+	+	+	+	+	+	+	+	+
The baseline study sample is adequately described for key characteristics.	+	+	+	+	-	+	+	+	+	+	-	+
Study Attrition												
Response rate is adequate.	+	+	+	+	+	+	+	+	+	+	+	+

Attempts to collect information on participants who dropped out of the study are described.	N/A: no loss to follow-up reported	-	N/A: no loss to follow-up reported	-	N/A: no loss to follow-up reported	-	-	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported	+	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported
Reasons for loss to follow-up are provided.	N/A: no loss to follow-up reported	-	N/A: no loss to follow-up reported	+	N/A: no loss to follow-up reported	+	-	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported	+	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported
Participants lost to follow-up are adequately described for key characteristics.	N/A: no loss to follow-up reported	-	N/A: no loss to follow-up reported	-	N/A: no loss to follow-up reported	-	-	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported	-	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported
There are no important differences between key characteristics and outcomes in participants who completed the study and those who did not.	N/A: no loss to follow-up reported	U	N/A: no loss to follow-up reported	U	N/A: no loss to follow-up reported	U	U	N/A: no loss to follow-up reported	N/A: no loss to follow-up reported	- Excluded women were younger than included women.	U	N/A: no loss to follow-up reported
Prognostic Factor Measurement												
A clear definition or description of the prognostic factor measured is provided.	+	+	+	+	+	+	+	+	+	+	~	+
Continuous variables are reported or appropriate cut-points are used.	+	+	+	+	+	+	+	+	+	+	+	+
An adequate proportion of the study sample has complete data for prognostic factors. The method and	+	+	+	+	+	+	+	+	+	+	+	+

setting of measurement are the same for all study participants. Appropriate methods are used if imputation is used for missing prognostic factor data.												
Outcome Measurement												
A clear definition of the outcome of interest is provided, including duration of follow-up and level and extent of the outcome construct.	+	+	+	+	+	+	+	+	+	+	+	+
The outcome measure and method used are adequately valid and reliable to limit misclassification bias.	+	~	+	+	+	+	+	+	+	+	+	+
The method and setting of measurement are the same for all study participants.	+	+	+	+	+	+	+	+	+	+	+	+
Confounding Measurement and Account												
All important confounders including treatments are measured.	-	-	-	-	-	-	-	+	-	-	-	-

Clear definitions of the important confounders measured are provided.	+	-	-	-	-	-	-	+	+	-	-	-
Measurement of all important confounders is adequately valid and reliable.	~	~	~	~	U	~	-	+	+	+	-	+
The method and setting of confounding measurement are the same for all study participants.	+	+	U	U	U	+	+	+	+	+	-	+
Appropriate methods are used if imputation is used for missing confounder data.	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	N/A: no imputation reported	+
Important potential confounders are accounted for in the study design.	-	+	+	+	-	U	+	+	+	+	-	+
Important confounders are accounted for in the analysis.	-	+	+	+	-	U	+	+	+	+	-	+
Analysis												
There is sufficient presentation of data to assess the adequacy of the analysis.	+	+	+	+	-	~	-	-	+	+	~	+
The strategy for model-building (i.e., inclusion of variables) is appropriate and is based on a	+	+	+	+	-	+	~	+	+	+	~	+

conceptual framework or model.												
The selected model is adequate for the design of the study.	+	+	+	+	-	~	~	+	+	+	-	+
There is no selective reporting of results.	+	+	+	+	+	+	+	-	+	+	+	+

+: Yes; -: No; ~: Partly; U: Unsure; N/A: Not Applicable