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Review article

The relationship between prenatal anxiety and gestational age: A systematic review

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ABSTRACT

Preterm birth poses a significant risk to short- and long-term infant health, and can have significant negative effects on maternal mental health. Increased levels of anxiety during pregnancy might be related to gestational age. Identifying potential risk factors for preterm birth may offer the opportunity for early intervention and reduce adverse outcomes. Ten databases, including empirical and grey literature, were searched. Articles were screened at title, abstract, and full-text review by two independent reviewers, and were quality assessed using the JBI critical appraisal tools. Forty-one studies were identified for inclusion in the review, published between 1990 and 2022. Data were narratively synthesised due to heterogeneity in study designs. Results of the data synthesis indicate there is an inverse relationship between anxiety and gestational age or preterm birth. This relationship may be dependent upon timing of assessment, and measure of anxiety used. Assessing anxiety at a single timepoint may not be as accurate as assessments across all three trimesters. Concerted efforts should be made to distinguish between spontaneous preterm birth and medically indicated preterm birth, as anxieties during pregnancy may present differently between the two groups. Future studies should consider the assessment of anxiety across trimesters to assess change in mood, as well as the use of pregnancy-specific measures alongside general measures to support intervention during pregnancy.

1. Introduction

In recent years, preterm birth (delivery at <37 weeks' gestation) [1] has been increasingly recognised as a significant public health issue [2], due to the adverse consequences which can persist into adulthood, such as neurodevelopmental and physical difficulties [3]. Estimates suggest approximately 15 million babies were born preterm in 2020, the majority of which were in lower income countries [3], although these rates may have been affected by the pandemic [4]. Of these, approximately 15 % were considered very premature (<32 weeks' gestation) [5], requiring an increased level and duration of neonatal care [3] which can be economically costly [6].

Many factors increase likelihood of preterm birth, including prenatal anxiety. This may be due to increased levels of corticotropin-releasing hormone [CRH] which increase when individuals feel anxious, which may in turn lead to earlier onset labour [7]. Women report anxiety in pregnancy often also report uncertainty and guilt over the loss of a perceived normal pregnancy [8]. A recent review [9] indicates that more needs to done to improve measurement of anxiety because the evidence base behind many current screening scales is inadequate. For example, studies using self-report measures may indicate a higher prevalence rate of anxiety (approximately 22 %) compared to clinical diagnostic criteria (approximately 15 %) [10], even if it does not inherently imply inadequate screening.

Whilst women's experiences of threatened preterm labour have been synthesised [11], that study did not focus on specific experiences of

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anxiety, but rather perceptions of care. Similarly, anxiety in women with experience of mid-trimester loss (between 14 and 23 weeks' gestation) may also be important as their risk of preterm birth in subsequent pregnancies is higher [12]. To our knowledge, there has not yet been a synthesis of qualitative evidence relating to women's retrospective experiences of anxiety during pregnancy when they have given birth preterm.

Although several systematic reviews have been conducted, limitations in their design warrant an updated review. Firstly, broad adverse perinatal outcomes were considered, rather than preterm birth itself [13,14]. Although this was the aim, they are broader in scope and less detailed consideration has been given specifically to anxiety and preterm birth. Secondly, stress and anxiety have been used synonymously, despite being conceptually and physiologically different [15,16]. The most recent review [17], published in 2016, found that higher prenatal maternal anxiety was associated with preterm and spontaneous preterm birth. However, it only considered four empirical English-language databases, which may present an issue due to higher rates of preterm birth in low-income (usually non-English-speaking countries). Additionally, searches were last conducted in June 2015 and so this requires updating [18].

Therefore, the overall aim of this mixed methods systematic review was to provide a comprehensive summary of the existing literature surrounding the relationship between prenatal anxiety and gestational age. Our objectives were to investigate:

1) What is the relationship between prenatal anxiety and gestational age?
2) What are the experiences of prenatal anxiety in mothers with previous experience of preterm birth?
3) What are the experiences of prenatal anxiety in mothers with previous experience of mid-trimester loss?
4) What are the experiences of prenatal anxiety for mothers who are at risk of preterm birth?

2. Methods

The current systematic review was preregistered on PROSPERO in February 2023 (CRD42023383845) [19] and is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [20].

2.1. Eligibility criteria

Studies were eligible for inclusion if they included a sample of mothers of premature singletons or multiple births (22 - < 37 weeks gestation). Studies could include a term or postpartum sample as a comparison to the prenatal sample, but the prenatal sample must have been analysed separately. Anxiety needed to have been measured during the prenatal period. We did not include other disorders related to anxiety (e.g., OCD, PTSD, panic disorder) in the search strategy as they have previously been reported as having unique clinical features, a distinct idiopathic profile, and/or a high prevalence of comorbidity which further obscures the symptoms of anxiety [21–23]. Whilst in the DSM IV, OCD was classified as an anxiety disorder, in the DSM V OCD classified as an *Obsessive-Compulsive Related Disorder* distinct from anxiety. Similarly, whilst phobia is still classified under anxiety disorders, it can only be diagnosed in the presence of a specific object or situation, whereas generalised anxiety is distinct as it is characterised by excessive anxiety and worry about a number of events or situations. Anxiety assessed postpartum could only be included if this was retrospective and only accounted for the prenatal period. Generalised Anxiety Disorder was included in the searches as it is commonly used in perinatal, specifically pregnant populations [24]. For this reason, GAD was thought important to be included compared to other distinct anxiety disorders. For full details, please see published protocol or *Supplementary Table 3*.

2.2. Information sources

Databases searched included empirical and grey literature, as well as theses/dissertations. Databases were searched in February and March 2023 and included a range of psychological, clinical and allied health databases (please see the published protocol for full details [19]). Searches included articles in press, as well as published works. The search strategy can be found in *Supplementary Table 4*.

2.3. Selection process

Initial searches were conducted by one author [SW] and exported to Rayyan [25], a website to streamline the inclusion and exclusion process when conducting systematic reviews. All reports were initially screened by title, abstract, and full-text by one author [SW]. The wider team ensured 100 % of reports were screened at each stage, according to the inclusion and exclusion criteria (title, abstract, and 10 full-text [NC]; 20 full-text [JM]; 11 full-text [OP]).

All titles and abstracts were written in English, however one article which went to full-text review was written in Spanish and was independently translated using forward-backward translation processes into English by a senior bilingual perinatal researcher. Discrepancies were agreed between extractors [SW, NC, JM, OP]; with any which could not be resolved being referred to a more senior author for arbitration [VF].

2.4. Data collection process and data items

Data extraction for articles which went to full-text screening were recorded on a Microsoft Excel spreadsheet with sub-headings, including: study aim, sample population/size, outcome measures, and study findings. For all sub-headings, please see the published protocol [19] and *Supplementary Table 5*.

2.5. Synthesis methods

A narrative synthesis [26] was deemed most appropriate to synthesise the data given heterogeneity in study designs, measures used, timings of assessments, and grouping of gestational age as a variable. Furthermore, given the extensive heterogeneity identified within the studies, meta-analyses were not deemed viable. Evidence for heterogeneity includes differences in study populations, recruitment methods, measurement, timing of outcome measurements, and analytical methods, including adjustment for confounding variables [27]. With respect to the synthesis, it was an analytic decision to focus on the measurements, as most research groups will seek to use tools to measure mental health, rather than individual constructs of the disorder of interest per each tool; hence the reporting in this review will follow synthesis by tool used.

2.6. Reporting Bias assessment

All studies meeting criteria for full-text inclusion were all independently screened using the relevant Joanna Briggs Institute (JBI) critical appraisal tool [28], dependent upon study design. This is a deviation from the published protocol [19], which initially identified that critical appraisal would be conducted using the Mixed Methods Appraisal Tool (MMAT) [29], because after all full-text articles were screened it was deemed more appropriate to use the JBI critical appraisal tool. This was because no qualitative studies were identified, and most study designs were largely limited to cohort studies.

3. Results

3.1. Study selection

Initial searches garnered 2579 articles (seven of which were from

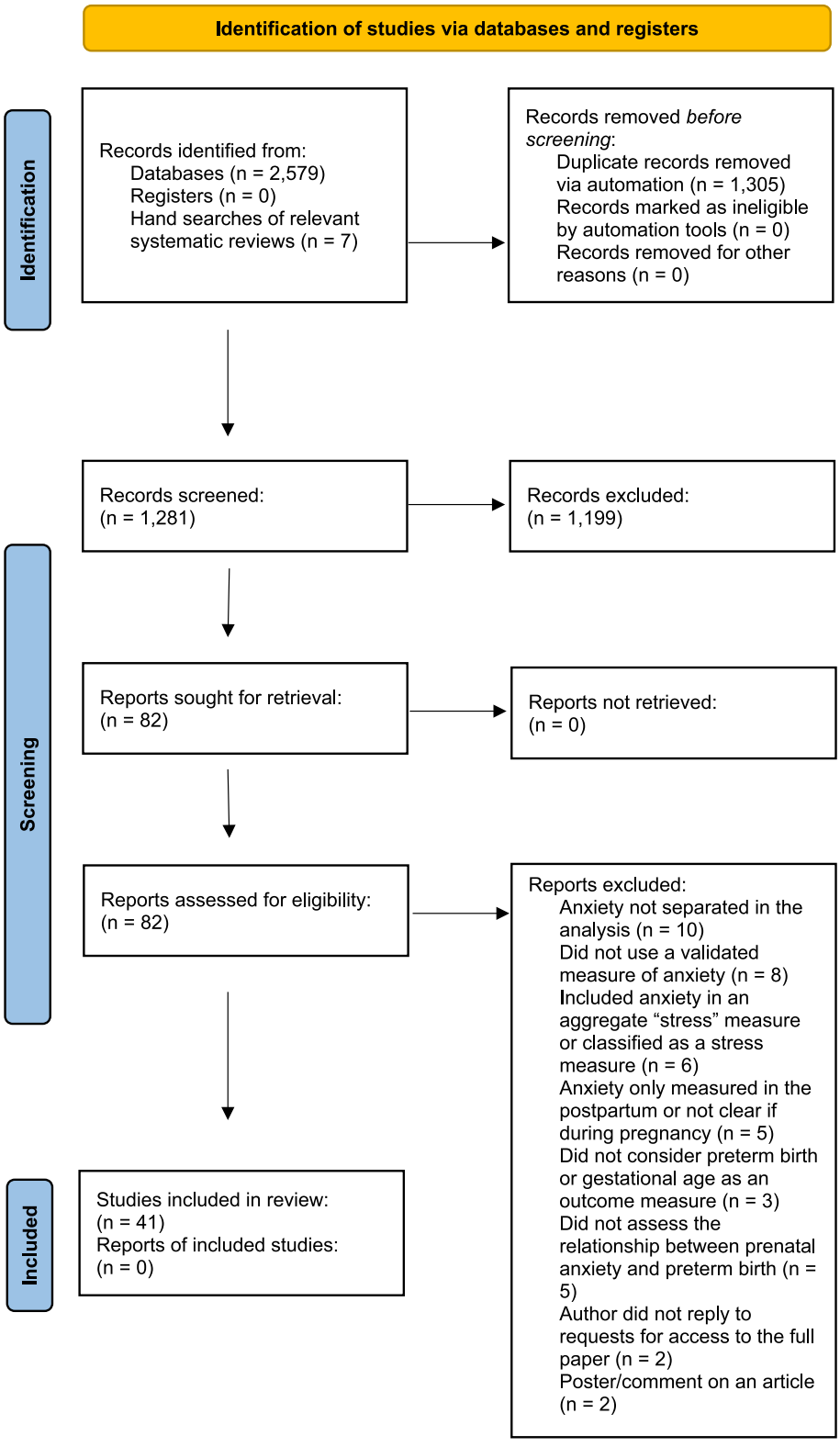

Fig. 1. PRISMA 2020 Flow Diagram.

hand searches of relevant systematic reviews). After the removal of duplicates, 1281 articles were screened at title and abstract stage, with 82 articles screened for full-text review. Of these, 41 were included in the current review. See Fig. 1: PRISMA flow diagram. Of note, whilst we have four objectives to this review, the lack of available qualitative data in the literature-base rendered it impossible to address the final three objectives, meaning only the first aim of this study is reported upon in the results and discussion.

3.2. Study characteristics

Studies included were published between 1990 and 2022, with

sample sizes ranging from 55 to 91,165 (N = 128,696), and were predominately conducted in the USA (n = 9) [30,31,32,33,34,35,36,37,38], Canada (n = 3) [39,40,41], or Peru (n = 3) [42,43,44]. A range of different analyses were used throughout the studies; adjusted analyses were reported over unadjusted analyses where available, and this is made clear when synthesising. Included articles were synthesised narratively according to psychometric measure of anxiety; pregnancy-specific measures of anxiety; clinical measures of anxiety and/or structured clinical or diagnostic interviews; generalised measures utilising clinical cut-offs, and general measures of anxiety. See *Supplementary Table 1*.

Of the 41 studies included, 21 [45,46,33,47,48,49,50,34,40,51,52–54,55,35,36,44,56–59] demonstrated no relationship between prenatal anxiety and gestational age, whilst 19 [30,39,60,61,31,32,42,43,62,63,64,65,66,37,41,67–70] indicate a negative relationship between prenatal anxiety and gestational age; one [38] indicated a positive relationship.

3.2.1. Reporting bias assessment

One study [43] was assessed using the case-control checklist from the JBI; the remaining 40 [30–32,39,45,46,60,61,33,42,47–49,50,62,34,40,51,63,64,65,52–54,66,55,35–38,41,44,56–59,67–70] were assessed using the checklist for cohort studies. No studies were excluded from the review; quality assessment was used to aid discussion about quality of studies and validity of findings. Generally, studies were of high quality. Further details are shown in *Supplementary Table 2*.

3.2.2. Pregnancy-specific measures of anxiety

Eight studies used a pregnancy-specific measure of anxiety [30–32,39,45,46,60,61], with four measures including the: Pregnancy Specific Anxiety Scale [PSA] [71] (n = 2) [30,60]; Pregnancy Related Anxiety Scale [PrAS] [72] (n = 4) [31,39,45,61]; Lederman Prenatal Self-Evaluation Questionnaire-Short Form [73] (n = 1) [32]; and Pregnancy and Childbirth Related Fears Questionnaire [74] (n = 1) [46]. Of these, five [30,39,60,61,32] identified some relationship between prenatal anxiety gestational age or preterm birth, whilst three did not [31,45,46].

3.2.2.1. Pregnancy-specific anxiety scale [71]. Of the two studies [30,60] which utilised the PSA, both found a significant association between gestational age/preterm birth and pregnancy-specific anxiety. The first study [30] assessed anxiety at three prenatal visits to examine change in pregnancy-specific anxiety and found an increase was significantly associated with shorter length of gestation ($\beta = -0.534$, SE = 0.254, $p = 0.034$) after adjusting for confounders. Whilst the authors considered a wide range of potentially confounding variables, they did not consider clinical diagnoses of anxiety.

Similarly, another study [60], using a prospective cohort design, assessed anxiety across three trimesters and found change in pregnancy-specific anxiety was also associated with preterm birth (outcome); whilst second-trimester anxiety was not related to preterm birth, third trimester anxiety was. However, it should be noted that although women with high risk factors for preterm birth were excluded from the study, there was no control for potential confounding variables in the analysis, and it is unclear whether appropriate statistical analyses were used.

3.2.2.2. Pregnancy related anxiety scale [72]. Four studies [31,39,45,61] used the PrAS. In two studies [39,61], after adjusting for covariates, pregnancy-specific anxiety was associated with shorter gestational length ($\beta = -0.82$, SE = 0.26, $p = 0.002$, $\Delta R^2 = 0.03$) and an increased risk of preterm birth ($\beta = 2.15$, SE = 0.79, $p = 0.007$, OR = 8.54) [39]. However, the authors did not control for prior preterm birth, and the sample consisted of highly educated, predominantly white women which may limit generalisability. Prenatal anxiety in the third trimester for Latina women only was associated with gestational age (b = −0.93, SE = 0.30, F = 9.62, $p = 0.002$, βx = −0.492), with a one standard deviation increase in anxiety at 31 weeks associated with a gestation reduced by 0.492 weeks [61]. This study was of high quality, controlling for a wide range of potential covariates.

However, despite another study [45] also assessing change in pregnancy-specific anxiety across two points in the second trimester, it did not predict preterm birth. Although an individual subscale (concerns/worries about fetal health) was significantly associated with preterm birth, this became non-significant in the adjusted model. Differences in results may be due to the low rate of preterm birth in the overall sample.

The final study [31] that used the PrAS alongside a general measure, described elsewhere. Participants were assessed at 18–20 weeks' gestation and 30–32 weeks' gestation, and pregnancy-specific anxiety was not a significant predictor of preterm birth at either assessment. Similarly to the above, there was a small number of overall preterm births in the sample, and the analysis only controlled for race and parity, which may explain the differences in results.

3.2.2.3. Lederman prenatal self-evaluation questionnaire – short form [73]. One study [32] used the Short-Form of the Lederman Prenatal Self-Evaluation Questionnaire and found that a rise of 1/10 unit of the slope in three prenatal anxiety dimensions (acceptance of pregnancy, preparation for labour, and fear of pain helplessness and loss of control in labour) resulted in an increased odds ratio for preterm birth by 37 % (aOR = 1.37, $p = 0.01$, CI 1.09–1.73), 60 % (aOR = 1.60, $p = 0.002$, CI = 1.18–2.16), and 54 % (aOR = 1.54, $p = 0.015$, CI = 1.09–2.18), respectively [32]. However, it should be noted that half of the sample were receiving an intervention for anxiety at the time of recruitment.

3.2.2.4. Pregnancy and childbirth related fears questionnaire [74]. The only study utilising the PCRFQ [46] demonstrated preterm labour was not significantly associated with pregnancy-specific anxiety after adjusting for potential confounders. However, there was a low overall rate of preterm delivery in the sample. The authors also note that a large number of predictors in the analyses may have increased the likelihood of a Type 1 error.

3.2.3. Clinical measures of anxiety and/or structured clinical or diagnostic interviews

Three studies [33,47,48]assessed participants using a clinical measure of anxiety: the Primary Care Evaluation of Mental Disorders [PRIME-MD] [75] (n = 1) [47]; the World Mental Health Composite International Diagnostic Interview [76] (n = 1) [33]; the Structured Clinical Interview for the DSM-IV [77] (n = 1) [48]. No study found a significant relationship between prenatal anxiety and gestational age or preterm birth.

3.2.3.1. Primary care evaluation of mental disorders [75]. The first study [47] assessed probable diagnosis of anxiety and found anxiety was not associated with either overall preterm birth or spontaneous preterm birth after adjusting for a number of demographic confounders. Although the overall study was of high quality, psychiatric diagnoses were only made at one point during pregnancy and only three women diagnosed with antenatal anxiety disorder gave birth preterm.

3.2.3.2. World mental health composite international diagnostic Interview [76]. Similarly, another study [33] assessed probable psychiatric diagnoses of GAD and after adjusting for confounding demographic and obstetric characteristics, there was no association between GAD and preterm birth at less than 28 weeks' gestation. Whilst the authors also assessed anxiety using the EPDS-3A, it was only reported in the supplementary materials as a sensitivity analysis, so is not described further. The overall study was of high quality, although differing results may be

because preterm births were only considered if they occurred prior to 28 weeks' gestation. Additionally, participants only required one month of symptoms to be diagnosed with anxiety, rather than the usual six months.

3.2.3.3. Structured clinical interview for the DSM-IV [77]. Women with psychiatric diagnoses of GAD were assessed and no significant differences were found between women with anxiety compared to women with no psychiatric diagnoses and gestational age [48]. However, there was no consideration of potential confounding variables in the analysis.

3.2.4. Generalised measures utilising clinical cut-offs

Five studies [42,43,49,50,52] used generalised measures according to clinical cut-offs, so are included here (Depression Anxiety and Stress Scale-21-item [DASS-21] [78] (n = 1) [43]; Hospital Anxiety and Depression Scale-A [HADS-A] [79] (n = 2) [50,52], and the Generalised Anxiety Disorder 7-item scale [GAD-7] [80] (n = 2) [42,49]. Of these, two [43,42] found a significant relationship but the other three [50,49,52] did not.

3.2.4.1. Depression anxiety and stress Scale-21-item [78]. One study [43] included in the review was the only case control study, with cases consisting of women who had experienced spontaneous preterm birth and controls consisting of women who had given birth at term, with anxiety during pregnancy assessed retrospectively. Anxiety disorders were classified as normal (<7), mild (8–9), or moderate-severe (≥10) measured by the DASS-21. Compared with the reference group, those with mild symptoms had increased odds of PTB (aOR = 1.72, 95 %CIs = 1.11–2.67), as did those with moderate-severe symptoms (aOR = 2.76, 95 %Cs = 1.83–4.16). Those with moderate-severe anxiety had increased odds of SPTL (aOR = 3.15, 95CIs = 1.99–5.01), with similar patterns in those with preterm premature rupture of the membranes [PPROM] (aOR = 2.39, 95 %CIs = 1.47–3.87). Similar associations with moderate symptoms according to severity of prematurity were also identified (<34 weeks aOR = 2.86, 95 %CIs = 1.76–4.63; 34- < 37 weeks aOR = 2.68, 95 %CIs = 1.69–4.26). The study was generally of high quality, adjusting for a wide range of potentially confounding variables, although it was not clear how long after birth the assessment of anxiety was conducted and the grouping of symptoms of anxiety in this manner may have reduced power.

3.2.4.2. Hospital anxiety and depression scale-A [79]. The first study using the HADS [50] defined HADS-A score of ≥8 as probable anxiety disorder according to DSM-IV and HADS sensitivity/specificity. However, gestational length was not significantly associated with anxiety disorder. Low rate of preterm birth in the overall sample, low power for the analysis of the relationship between anxiety disorder and gestational age, alongside no control for any pre-existing diagnosis of anxiety should be considered when interpreting the results.

The second [52] assessed women with pregestational diabetes and found no significant differences between anxiety scores between preterm and term mothers, or anxiety scores ≥8. The study did not control for confounders, and only included women with pregestational diabetes who may be aware of the increased risk of preterm birth. The authors also acknowledge that, they only reported parametric tests despite non-normally distributed data.

3.2.4.3. Generalised anxiety Disorder-7-item [GAD-7] [80]. The first study [42] utilising the GAD-7 used a cut-off of ≥7 to identify generalised anxiety, and whilst the odds of preterm birth were not increased for women with anxiety, they delivered infants 0.15 weeks earlier than those without anxiety (95 %CIs = 0.27–0.04, p = 0.010). However, approximately 6 % of the overall sample gave birth preterm.

Similarly, another [49] found no significant association between anxiety and preterm birth, although the authors acknowledge the study may have low statistical power and anxiety was only considered at a singular timepoint.

3.2.5. General measures of anxiety

Twenty six studies [31,62,34,40,51,63,64,65,66,53,54,55,35–38,41,44,56–59,67–70] used a general measure of anxiety, with a total of ten different measures including the: Hopkins Symptoms Checklist [HSCL] [81] (n = 1) [62]; Edinburgh Postnatal Depression Scale – Anxiety Subscale [EPDS-3A] [82] (n = 2) [51]– [40]; Multiple Affect Adjective Check List – State Form [MAACL-S] [83] (n = 1) [34]; Zung Self-Rating Anxiety Inventory [SAS] [84] (n = 2) [63,64]; State Trait Personality Inventory [STPI] [85] (n = 1) [65]; the DASS-21 [78] (n = 1) [66]; HADS-A [79] (n = 1) [53]; General Health Questionnaire [GHQ] [86] (n = 1) [54]; Abbreviated Scale for the Assessment of Psychosocial Status in Pregnancy [ASAPSP] [87] (n = 1) [55]; and the State Trait Anxiety Inventory [STAI] [88] (n = 15) [31,35–38,41,44,56–59,67–70]. Of these, 13 found some relationship between prenatal anxiety and gestational age/preterm birth [31,62,63,64,65,66,85,37,38,41,67–70]. The remaining 13 did not [34,40,51,53,54,55,35,36,44,56–59].

3.2.5.1. Hopkins symptoms checklist [HSCL] [81]. One study [62] used two short-forms of the HSCL [81] (SCL-5 at 17 weeks' gestation and SCL-8 at 30 weeks' gestation) and after adjusting for potential confounders found anxiety at 17 weeks' was not significantly associated with gestational age at delivery, but anxiety at 30 weeks (β = −1.14, 95 %CIs = −1.64—0.64), or anxiety at both 17 and 30 weeks (β = −1.52, 95 %CIs = −2.15—0.89) was. When data were assessed using a sibling comparison design, only anxiety at 30 weeks was significantly associated with gestational age (β = −1.11, 95 %CIs = −1.82—0.40). The study was generally of high quality and controlled for a number of demographic confounders, although the authors did not consider any potential diagnoses of anxiety prior to pregnancy and it is unclear if standardised or unstandardised coefficients were reported.

3.2.5.2. Edinburgh postnatal depression scale – anxiety subscale [EPDS-3A] [82]. Two studies [40,51] used the anxiety subscale of the EPDS [82] and indicated a cut off of ≥6 indicative of anxiety.

The first [51] assessed women during early (M = 17.4, SD = 4.9 weeks) and late pregnancy (M = 30.6, SD = 2.7 weeks) and found no significant association between anxiety and preterm birth. The authors acknowledge that the relatively low sample size has low statistical power and the predominantly white, highly educated sample limits generalisability.

The second [40] also found no significant association with anxiety and preterm birth. Some medical and obstetric risk factors were not controlled for in the analysis.

3.2.5.3. Multiple affect adjective check list – state form [MAACL-S] [83]. The only study using the anxiety scale of the MAACL-S [83] in women attending their first prenatal visit found no significant correlation between anxiety and preterm birth [34]. The sample is only representative of high-risk women and is limited by the relatively small sample size.

3.2.5.4. Zung self-rating anxiety inventory [SAS] [84]. One study [63] using the SAS [84] and found a significant difference between anxiety levels when comparing those who gave birth at term with those who gave birth preterm (p < 0.001). However, the small sample size of only 60 women, and a low incidence of preterm birth, and there was no consideration of potentially confounding variables.

Another study [64], assessed anxiety at three separate timepoints (25–29 weeks', 30–34 weeks', and > 34 weeks') and found that only anxiety assessed between 25 and 29 weeks' predicted preterm birth (β = −0.28, Wald = 6.31, p = 0.01, Exp(β) = 0.76), but not anxiety at other time periods. However, two items were removed from the SAS after the

first timepoint due to low correlation coefficients, so an 18-item version was used at subsequent time periods. Additionally, demographic variables were controlled for, but a low proportion of the sample gave birth preterm.

3.2.5.5. State trait personality inventory [STPI] [85]. The only study [65] using the anxiety subscale of the STPI [85] assessed women at all three trimesters. After controlling for confounders, anxiety in the first trimester did not predict gestational age, however third trimester anxiety did (R^2-change = 0.009, unstandardised B = -0.23, $p < 0.01$). In women who reported severe anxiety during all three trimesters, gestational age was significantly shorter compared to women who did not report severe anxiety in any trimester ($F(3, 864) = 2.80$, $p < 0.05$). However, although controlling for a wide range of demographic and medical confounders, it should be noted that third trimester anxiety was assessed retrospectively after birth.

3.2.5.6. Depression anxiety stress scale-21 [DASS-21] [78]. One study [66] utilised the anxiety subscale of the DASS-21 [78] in a prospective cohort study recruiting participants from the East and West coasts of Malaysia. Although anxiety was not significantly associated with preterm birth overall, it was an independent risk factor for PTB in the East coast only (aRR = 2.49, 95 %CIs = 1.16–5.36), which is a poorer, less urbanised area. Although there was a consideration of potentially confounding variables in the analysis, women were only recruited and assessed in their third trimester of pregnancy, and a low percentage of the overall sample gave birth preterm.

3.2.5.7. Hospital anxiety and depression scale [HADS] [79]. The only study using the HADS in this context [53] found HADS anxiety score was not a significant predictor of preterm birth in women assessed between 24 and 28 weeks' gestation. However, consideration of potentially confounding variables was unclear.

3.2.5.8. General health questionnaire [GHQ] [86]. The only study that assessed anxiety using the GHQ [86] at 28 and 36 weeks gestation found no significant relationship between anxiety and preterm birth [54]. Only white women were eligible for inclusion in the study, which limits generalisability of the findings, and the proportion of women who gave birth preterm in the overall sample is unclear.

3.2.5.9. Abbreviated scale for the assessment of psychosocial status in pregnancy [ASAPSP] [87]. Although the name suggests the ASAPSP is specific to pregnancy, the measure was adapted from, and validated based on, general measures of anxiety, so is included here instead. One study [55] used it to assess women during their second trimester, but found no significant difference in anxiety between participants who scored in the ≤25th percentile, or those in the ≥25th percentile who had experienced spontaneous preterm birth, or between continuous scores and spontaneous preterm birth. Anxiety was only assessed at a singular timepoint, and the sample predominantly consisted of black, low income, married women.

3.2.5.10. State trait anxiety inventory [STAI] [88]. The most utilised tool was the STAI [88], with 15 studies [31,35–38,41,44,56–59,67–70] including it, either separately, in its state or trait forms, or considering the scale as a whole. Of these, seven studies [35,36,44,56–59] found no relationship between preterm birth or gestational age, and anxiety.

The first study [67] split the STAI according to its factors and found factor one (state of nervousness, tension, anxiety, and restlessness) was associated with gestational age after the addition of confounders into the model ($\beta = 0.145$, $t = 2.250$, $p = 0.026$). However, anxiety was assessed retrospectively after birth, and there were no very premature births in the sample, which may limit generalisability.

When comparing state anxiety scores at 20–28 weeks' gestation, another [68] found a high state anxiety score ≥ 45 was associated with an increase in preterm delivery (RR = 3.1, 95 %CIs = 2.05–4.7). Mothers of premature infants also had higher trait anxiety scores comparative to mothers of term infants ($p < 0.001$). However, it was not clear how participants were recruited and there was no consideration of potential confounding variables.

Similarly, another study [41] assessed anxiety during the second (17–24 weeks') and third (34–36 weeks') trimesters with women with increased levels of anxiety having significantly greater odds of delivering preterm compared to those who had a decline (aOR = 2.35, 95 % CIs = 1.01–5.45, $p = 0.048$). For every decrease of one point on the anxiety scale, women had 4 % lower odds of delivering preterm infants (aOR = 0.96, 95 %CI 0.94–0.98, $p = 0.001$), however consistently anxious women were not at significantly greater odds of delivering preterm. The authors acknowledge that some estimates had wide confidence intervals which may be improved by an increase in sample size. Additionally, an analysis of the relationship between anxiety and categories of prematurity should also be considered.

In another study, when adjusting for all potential confounding variables, anxiety in the third trimester only was significantly associated with gestational weeks ($\beta = -0.05$, 95 %Cis = −0.08;-0.01, $p < 0.05$) [69]. However, when preterm birth was treated as a categorical variable, there was no significant association with anxiety. The sample consisted predominantly of women of high socioeconomic status [SES] and so may be more aware of potential risks during pregnancy, like preterm birth, which may elicit anxiety. Furthermore, the study combined a community-based and a high-risk sample which may be problematic as they may not be similar enough to analyse together.

Another study [37] measured anxiety in women at <21 weeks of gestation and, after adjusting for potential covariates, each standard deviation increase in anxiety was associated with a gestational age that was 1.6 days shorter ($\beta = -1.2$, SE = 0.65, $p = 0.06$) whilst participants with anxiety scores >12 had 3.3 days shorter gestations ($p = 0.03$). This effect may be increased in African American women as for each standard deviation increase in anxiety, gestational age decreased by 3.7 days in African American women ($\beta = -3.7$, SE = 1.30, $p < 0.01$); for those with scores >12, gestation was 8.2 days shorter ($p < 0.01$). Whilst the authors controlled for a range of potential covariates, anxiety was only assessed at one antenatal assessment.

In another study [31], when anxiety was assessed during the second (18–20 weeks') and third (30–32 weeks') trimesters, change in state anxiety were not significantly associated with preterm delivery, nor was anxiety at either gestational timepoint. However, after adjusting for potential confounders, participants with an increase in state anxiety were more than twice as likely to have delivered preterm (OR = 2.49, 95 %CI = 1.24–4.98) and women who delivered preterm were significantly more likely to show increases in state anxiety between the timepoints $\chi^2(1, 415) = 6.3$, $p < 0.05$.

Similarly, another study [70] measured anxiety at <20 weeks and found that compared with non-anxious women (depressed or not depressed), there was a significant difference in mean gestational age ($p = 0.06$), and spontaneous preterm birth (OR = 1.78, 96 %IC = 0.97–3.21, p = 0.06) in all anxious women, but not between medically indicated preterm birth (OR = 1.78, 96 %IC = 0.97–3.21, $p = 0.74$) or preterm birth (OR = 1.40, 96 %IC = 0.85–2.30, $p = 0.19$). Overall, the study was of high quality and was one of the few considering both medically indicated and spontaneous preterm birth in this review.

Contrary to the others, the final study using the STAI [38] found state anxiety, assessed as dispositional and stable, was positively correlated with gestational age ($p < 0.001$). Only seven women in the sample gave birth preterm, but of these the mean values for anxiety were significantly lower ($p < 0.05$). There was also a significant association between low anxiety in the second trimester and preterm delivery ($p = 0.013$) as well as the third trimester ($p = 0.019$). The sample size was small ($n = 88$) which may limit statistical power, and which confounding variables, and at which step they were added to the model, was unclear.

4. Discussion

This systematic review aimed to investigate the relationship between prenatal anxiety and gestational age at delivery, and consider the experiences of prenatal anxiety for mothers who go on to give birth prematurely. It also aimed to investigate the experience of prenatal anxiety in mothers who have previously experienced a mid-trimester loss or who are at risk of preterm birth. There was no qualitative literature included in the review, so only the first aim could be addressed.

Of the 41 studies included in the review, 19 [30,39,60,61,31,32,42,43,62,63,64,65,66,37,41,67–70] indicate a negative relationship between prenatal anxiety and gestational age (preterm birth); one [38] indicated a positive relationship. However, heterogeneity in study designs, control for confounders, or lack thereof, and differences in measures and timing of assessment, limits the ability to make firm conclusions about the extent to which there is a relationship between prenatal anxiety and gestational age.

4.1. Assessment of anxiety

Most studies (n = 26) [31,62,34,40,51,63,64,65,66,53,54,55,35–38,41,44,56–59,67–70] used a generalised measure of anxiety and, of these, 13 studies [31,62,63,64,65,66,37,38,41,67–70] indicated a relationship between anxiety during pregnancy and gestational age or preterm birth. The majority of studies (n = 15) [31,35–38,41,44,56–59,67–70] used the STAI [88], of which, eight [31,37,38,41,67–70], indicated increased anxiety during pregnancy may increase the risk of giving birth preterm. These studies were generally of high quality, controlling for a range of confounders. However, one study [38] indicated anxiety was positively correlated with gestational age, although a limited sample size and less than 1 % of the total sample giving birth preterm means results should be interpreted with caution. Inconsistency in findings may be due to limitations of the studies themselves, with recent research indicating the STAI may not be suitable for use in this population, as it may not accurately conceptualise anxiety in pregnant women because it was intended for use in general adult populations [89]. Adjustment for potential confounders was not consistent across studies which may also explain the findings of this review. Whilst most studies included this information [31,44,58,36,67,37,38,41,69,70], which confounders were added to the model was inconsistent, and in other studies the consideration of potential confounders was either unclear [56,59,38] or not done [57,35,68].

In total, three studies [33,47,48] utilised clinical diagnoses of anxiety, and a further five [43,50,42,49,52] used generalised measures with clinical cut-offs. Despite mixed evidence to support the use of the GAD-7 in this population, including poor screening accuracy [90], National Institute for Health and Care Excellence [NICE] recommendations for its use have persisted.

Increasingly, pregnancy-specific anxiety has been recognised as its own construct of anxiety, which may require measurement tools that are more specific than general measures, such as the GAD-7. Whilst it has been argued pregnancy-specific anxiety and generalised anxiety can influence one another [91], pregnancy-specific anxiety is relatively under-recognised despite its possible persistence postnatally, which may affect the mother-infant relationship [92]. The ability to target poor psychological health or reactions to events (e.g., anxiety surrounding birth or breastfeeding [93]), and intervene may reduce adverse perinatal outcomes, which a generalised measure cannot elicit. This may also go some way to explain why no clinical measures of anxiety included in the review found a significant relationship between prenatal anxiety and gestational age/preterm birth, as it has been suggested that pregnancy-specific anxiety elicits a different emotional response than generalised anxiety, and so may have a differing clinical profile [92]. Therefore, future studies may benefit by measuring pregnancy-specific anxiety alongside other measures.

4.2. Spontaneous PTB vs. medically indicated PTB

Nine [47,43,40,53,55,57,58,68,70] studies included in the review explicitly investigated spontaneous preterm labour and one [70] distinguished between medically-indicated or spontaneous preterm birth. The remaining studies only specified they considered preterm birth or gestational age but did not distinguish between spontaneous or medically indicated preterm birth. Of the nine [47,43,40,53,55,57,58,68,70], three [43,68,70] indicated a significant inverse relationship between anxiety and spontaneous preterm birth. Distinguishing between spontaneous and medically indicated preterm labour is important as the unexpectedness of birth is often cited as one of the main reasons for psychological distress in the postpartum [94,95], whereas this may not be as pertinent in medically indicated deliveries.

4.3. Timing of assessment

Consideration of timing is important to consider, particularly as women in their third trimester may be more aware of their own risk status which may increase anxiety and, subsequently, the risk of preterm birth. Similarly, women in their first trimester may be more anxious about survival of the infant [96]. Specific anxieties may differ across trimesters, so use of a pregnancy-specific measure may be more accurate. It has been suggested that a ‘one-off’ assessment of anxiety is not sufficient, and assessment should be repeated [97]. As such, future studies should continue to assess anxiety across multiple timepoints throughout pregnancy. Further to this, extant guidelines [98] already have suggested this and so this systematic review provides further evidence for the need to further support widespread implementation.

4.4. Clinical implications

In the UK, the NHS does not currently employ a standardised, specific screening tool for pregnancy-specific anxiety, which is concerning given its distinct clinical aetiology. Although mental health is encouraged to be asked about at every contact, this is not happening as standard [99]. As such, concerted efforts must be made to ensure that mental health in pregnant women is seen as a priority. As pregnancy-specific anxiety is characterised by anxieties related directly to the pregnancy, given its link with adverse neonatal outcomes, consideration of the disorder in this context is essential. Specifically, even in specialist preterm birth clinics, mental health is not routinely monitored [100]. This gap in care in problematic, given that preterm birth is itself both a potential consequence of pregnancy-specific anxiety and a unique stressor that can exacerbate mental health difficulties, particularly anxiety, after birth [101,102]. Furthermore, consideration should be given at a Governmental level to prioritise specialised care for women at risk of preterm birth, as it is well established that this can identify those who are most likely to suffer both physical and mental health co-morbidity during their pregnancy [100].

4.5. Strengths, limitations, and future directions

All studies were independently screened by two authors (SW; NC/JM/OP) and so data extraction can be considered robust. A wide range of psychological and medical/allied and public health databases were searched, and no studies were excluded based on study design or language. We would recommend having a structured protocol for reconciling screening and extraction disagreements, despite not having any in this review. Whilst included studies were predominantly from high-income countries [30,39,31,32,46,33,47,50,62,34,40,52–54,57,35,36,58,59,67,37,38,41,69,70], those from upper- [60,45,42,48,43,64,66,44,68] and lower-[49,63] middle income countries were also included (countries for five studies [61,51,65,55,56] were unclear). However, no qualitative studies were included, which is concerning given anxiety during pregnancy is multi-faceted and complex, and may

not be accurately conceptualised by quantitative measurement. Future studies should consider the assessment of anxiety across trimesters to assess trajectories of change, as well as the widespread use of pregnancy-specific measures alongside general measures to support intervention during pregnancy, which may reduce the likelihood of adverse birth outcomes, such as preterm birth. It was not possible to conduct a meta-analysis due to the vast heterogeneity in study designs. Furthermore, a more comprehensive review, including other anxiety disorders, will be required. Future research should consider standardisation of confounders, measures, and timing of assessment to aid a future meta-analytic study.

4.6. Conclusion

The findings of this review suggest some relationship between prenatal anxiety and gestational age. However, difference in study design including varying control for confounders, differing measures of anxiety, and timing of assessment limit the ability to make firm conclusions. Finally, qualitative assessment of prenatal anxiety is crucial to understand not only how anxious someone is, but how said anxiety is manifesting and is experienced. However, whilst we have four objectives to this review, the lack of available qualitative data in the literature-base rendered it impossible to address the final three objectives, meaning only the first aim of this study is reported upon in the results and discussion.

CRediT authorship contribution statement

Semra Worrall: Writing – original draft, Visualization, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Naomi Carlisle:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Olivia Pike:** Writing – review & editing, Validation, Investigation, Formal analysis. **John Moffitt:** Writing – review & editing, Validation, Investigation, Formal analysis. **Jenny Carter:** Writing – review & editing, Methodology, Conceptualization. **Paul Christiansen:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Asma Khalil:** Writing – review & editing, Supervision, Methodology. **Sergio A. Silverio:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Victoria Fallon:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Ethical statement

Not applicable.

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Declaration of competing interest

All other authors declare no conflict of interest.

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Appendix A. Supplementary data

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