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Review article

The effects of maternal depression, anxiety, and perceived stress during pregnancy on preterm birth: A systematic review

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ABSTRACT

Background: Experiencing psychological distress such as depression, anxiety, and/or perceived stress during pregnancy may increase the risk for adverse birth outcomes, including preterm birth. Clarifying the association between exposure and outcome may improve the understanding of risk factors for prematurity and guide future clinical and research practices.
Aim: The aims of the present review were to outline the evidence on the risk of preterm associated with antenatal depression, anxiety, and stress.
Methods: Four electronic database searches were conducted to identify quantitative population-based, multi-centre, cohort studies and randomised-controlled trial studies focusing on the association between antenatal depression, anxiety, and stress, and preterm birth published in English between 1980 and 2013.
Findings: Of 1469 electronically retrieved articles, 39 peer-reviewed studies met the final selection criteria and were included in this review following the PRISMA and MOOSE review guidelines. Information was extracted on study characteristics; depression, anxiety and perceived stress were examined as separate and combined exposures. There is strong evidence that antenatal distress during the pregnancy increases the likelihood of preterm birth.
Conclusion: Complex paths of significant interactions between depression, anxiety and stress, risk factors and preterm birth were indicated in both direct and indirect ways. The effects of pregnancy distress were associated with spontaneous but not with medically indicated preterm birth. Health practitioners engaged in providing perinatal care to women, such as obstetricians, midwives, nurses, and mental health specialists need to provide appropriate support to women experiencing psychological distress in order to improve outcomes for both mothers and infants.

1. Introduction

Research has identified that amongst women who experience psychological adversities during pregnancy there is a trend towards sub-optimal birth outcomes, including mortality and morbidity, shorter gestation, and lower birth weight.[1] According to the World Health Organization, 2009, preterm birth (PTB) is the leading cause of infant mortality and, morbidity. Infants born preterm (<37 weeks of completed gestation) are at a greater risk of various health and developmental problems, and present a considerable emotional and economic cost to families, as well as significant implications for public-sector services. Despite decades of investigation, the incidence of preterm birth has not declined and its aetiology remains unexplored.

PTB has been linked to a complex cluster of overlapping biomedical, social and psychological factors. While some studies report no link between maternal mental health during pregnancy and birth outcomes,[2] there is emerging evidence of the relationship between maternal mental health during pregnancy and

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pregnancy outcomes, including PTB (for reviews see 1). However, evidence of the specific effects of antenatal depression, anxiety and stress on birth outcomes remains unclear and at times conflicting. Therefore, the main objective of this review is to identify and examine the impact of overall maternal psychological distress during pregnancy, specifically the three most prevalent diagnostic (clinical) and symptomatological (sub-clinical) presentations of psychological distress, i.e., depression, anxiety and perceived stress (referred to subsequently as DAS) during pregnancy.

Depression is one of the most common complications during pregnancy and the childbearing years. The prevalence of major depressive disorder defined by diagnostic criteria during pregnancy is 12.7%, while as many as 37% of women report experiencing depressive symptoms at some point during their pregnancy.[3] Anxiety is known to be more prevalent than depression at all stages of pregnancy although there is a high level of comorbidity of about 60% between the two.[3,4] Additionally, the way a woman perceives and interprets various stressful events in her environment during pregnancy has gained increasing research attention, especially in respect to the contribution to adverse birth outcomes.

Experiencing depression, anxiety, or stress (DAS) during pregnancy may expose both mother and infant to (1) many psychological risks, including an impaired bonding with the foetus and with the new-born, increased risk of poor psychological postnatal adjustment, postnatal depression, and (2) physiological consequences, including low birth weight, intra-uterine growth restriction, and preterm birth. This review will focus on studies reporting PTB, defined as birth prior to the completion of 37 weeks gestation.

It is likely that, beyond the established bio-medical factors, depression, anxiety and perceived stress may contribute in different ways to PTB, activating different pathways in the process. Furthermore, the co-morbidity of depression, anxiety and perceived stress may pose an even higher risk for PTB. Therefore, the secondary objective of this review is to examine the effects of depression, anxiety and perceived stress as individual and as combined exposures.

Additionally, it is recognised that the relationship between DAS and PTB and the interpretation of findings is expected to be influenced by the operationalisation of DAS and PTB, the antenatal measures used and potential modifying and confounding variables. Consequently, the third objective of this review is to critically consider these methodological influences in determining the relationship between DAS and PTB.

2. Methods

The protocol for the review was developed and agreed by the authors prior to commencement. It followed all aspects recommended in the reporting of systematic reviews, namely the PRISMA Checklist and MOOSE Guidelines.[5,6] Epidemiological studies (both observational and experimental) that explored the association between DAS during pregnancy and PTB were considered for this review. Depression and anxiety were conceptualised as defined by DSM-IV-TR criteria on mood disorders (2000). Stress was conceptualised as an individual's response to a stressful situation through a validated self-report measure of stress and not only the occurrence of specific stressors (such as daily, occupational, chronic, etc., stressors only). Principal summary measures for associations were odds ratios (OR), relative risks (RR), hazard ratios (HR), regression coefficients, and a discriminate predictive function. The protocol was not submitted for registration.

2.1. Eligibility criteria and search strategy

MEDLINE, CINAHL, PsycInfo, and Cochrane databases searches were conducted by the first author (AS), with the help of an experienced health sciences librarian (JD). Search terms, inclusion and exclusion criteria applied in the review can be found in Table 1.

All articles were entered into EndNote X6 (Thomson Reuters, Carlsbad, CA, USA). Subsequent manual searches were performed through reference lists of the papers and of other published reviews. A study selection table detailing inclusion and exclusion criteria (Table 1) was used by two reviewers (AS and FB), who independently judged a random sample of studies to enhance reliability of selection. Subsequently, studies that were under question for inclusion ($n = 20$) were re-examined by the second reviewer (FB). Of 1469 reviewed studies, 39 met the inclusion criteria and were selected for final quality assessment.

2.2. Assessment of quality and risk of bias

The methodological quality and risk of bias of each study were assessed using an adapted checklist developed by a knowledge synthesis group for the specific purpose of review of the evidence relating to determinants of preterm and low birth weight births.[7] The checklist is applicable across study types and details criteria and standards for selection, exposure assessment, outcome assessment, confounding factors, analytical, and attrition bias assessment with classifications ranging from *None* to *High*, and *Cannot Tell* (see Table 2). Adjustments were made regarding exposure and outcome descriptions, definitions criteria, and criteria for confounding factors, where the lowest (none) levels of bias were ascertained to studies that controlled for all common and adjusted confounders and high bias was assigned to studies that did not consider or report on any confounders. Overall bias

Table 1
Search terms, inclusion and exclusion criteria.

Search terms (keywords, index words, MeSH headings, and their combinations using Boolean AND/OR operators)	1. "in pregnancy" OR "in pregnant women" OR "during pregnancy" OR "whil* pregnant" OR prenatal OR antenatal OR prepartum OR antepartum; 2. anxiety OR depress* OR anxious OR stress* OR mental OR distress*; {Anxiety} OR {Anxiety Disorders} OR {Anxiety Management} OR {Depression (Emotion)} OR {Major Depression} OR {Stress} 3. preterm OR premature OR "early delivery" OR "early onset of labour" OR "early onset of labor" OR prematurity OR gestational age; {Premature birth}
Included	English-language articles published between 1980 and 2013 Quantitative primary research articles (population-based, multi-centre, cohort studies and randomised-controlled trials) Measured depression, anxiety and stress symptoms in all pregnant women by means of self-reported questionnaires or structured psychiatric interview Reported the use of validated diagnostic or screening tools to determine either one of depression, anxiety, or stress
Excluded	Reviews or theoretical papers Retrospective design was used to measure antenatal depression, anxiety or stress Duplicate articles using the same data Primarily focus was on the use of antidepressant medication, rather than the measurement and diagnosis of depression

Table 2
Quality assessment tool.

Bias	None	Low	Moderate	High	Cannot tell
Selection	• Consecutive unselected population • Sample selected from general population rather than a selected group • Rationale for case and control selection explained • Follow-up or assessment time(s) explained	• Sample selection form large population but no defined selection criteria • A select group of population based on race, ethnicity, residence, etc. studied	• Sample selection ambiguous but sample may be representative • Eligibility criteria not explained • Rationale for case and controls not explained • Follow-up or assessment time(s) not explained	• Sample selection ambiguous and sample likely not representative • A very select population studied making it difficult to generalise findings	–
Exposure assessment	• Direct interview with the mother during pregnancy regarding DAS • More than once during pregnancy	• Completion of self-report measure by the mother regarding DAS • Once or more during pregnancy	• Assessment of DAS from global dataset (National register, Vital statistics)	• Extrapolating data from population exposure sample or indirect method of assessment (not from mother but others)	–
Outcome assessment	• Assessment from hospital record, birth certificate • PTB defined as <37 weeks • Ultrasound or last menstrual period	• Assessment from administrative database (National register, Vital statistics) • PTB defined as <37 weeks • Ultrasound or last menstrual period	• Assessment from direct question to mother regarding length of gestation or with open-ended questions • Unclear cut-off point for gestational length	• Assessment form non-validated sources or generic estimate from overall population • Unclear cut-off point for gestational length	–
Confounding factor	• Controlled for all common adjusted confounders	• Only certain main confounders adjusted	• Very few (1–2) confounders were controlled for	• Not controlled for confounders	–
Analytical	• Analyses appropriate for the type of sample • Analytical method accounted for sampling strategy in cross-sectional studies • Sample size calculation performed and adequate sample studied	• Analyses not accounting for common statistical adjustment (e.g., multiple analyses) when appropriate • Sample size calculations not performed, but all available eligible patients studied • Sample size calculated and reasons for not meeting sample size given	• Sample size estimation unclear or only sub-sample of eligible participants studied	• Analyses inappropriate for the type of sample/ study	–
Attrition	• 0–10% attrition and reasons for follow-up loss explained • All subject from initiation of study to final outcome assessment were accounted for	• 0–10% attrition and reasons for follow-up loss not explained	• 11–20% attrition, reasons for follow-up loss not explained • >20% attrition reasons explained • All subjects form initiation to final assessment not accounted for	• >20% attrition reasons not explained	–

Adapted from Shah.[7]

assessment was determined as the most frequently occurring, highest level across the six categories. The *Cannot Tell* assessment was interpreted as a high level of bias. Discrepancies were resolved by a consensus between AS and FB, a process which reflected that undertaken by the checklist originators.

3. Findings

3.1. Description of studies

The study selection process is reported as recommended by the PRISMA group[5] in Fig. 1. The final 39 articles selected for review represented a total of 134 488 pregnant women. The majority of studies (27) were from the USA, and the remainder from Sweden (2), Denmark (2), France (2), Brazil (2), Canada (1), UK (1), Norway (1), and China (1). All studies employed prospective cohort study design and multivariate data analysis. Six studies drew upon large population-based data. Sample sizes varied from 88 to 63 395, and sampling ranged from convenient to systematic (random). Settings ranged from university hospital-based clinics, multi-centre studies, to public hospitals with antenatal clinics. Pregnancy outcome (PTB, and other) data were generally collected from medical charts. However, there were exceptions, and in these cases the data were collected directly from women by contacting them[8] but only after medical records were deemed unavailable.

3.2. Assessment of bias

Eighteen studies were assessed as exhibiting low overall methodological bias, 16 as having moderate bias, four studies deemed to have high bias, and one study was assigned as not biased (see Table 3). When moderate and high levels of assessed bias were combined and considered across the selected studies, the majority of studies exhibited selection bias (66%), and exposure assessment bias (54%). We aimed at presenting the reader with a complete picture of the current literature, thus the four studies with high levels of bias were not excluded at this stage, despite scoring highest on confounding factors, as they captured important information on the association between exposure and outcome variables. The remaining bias types were evident in the minority of studies with the proportion of studies exhibiting confounding factor bias assessed at 36%, followed by analytical bias (31%), outcomes assessment bias (28%) and attrition bias (10%). Within the studies with low and no bias, the most frequently occurring type of bias was again selection bias (47%) and exposure assessment bias (37%).

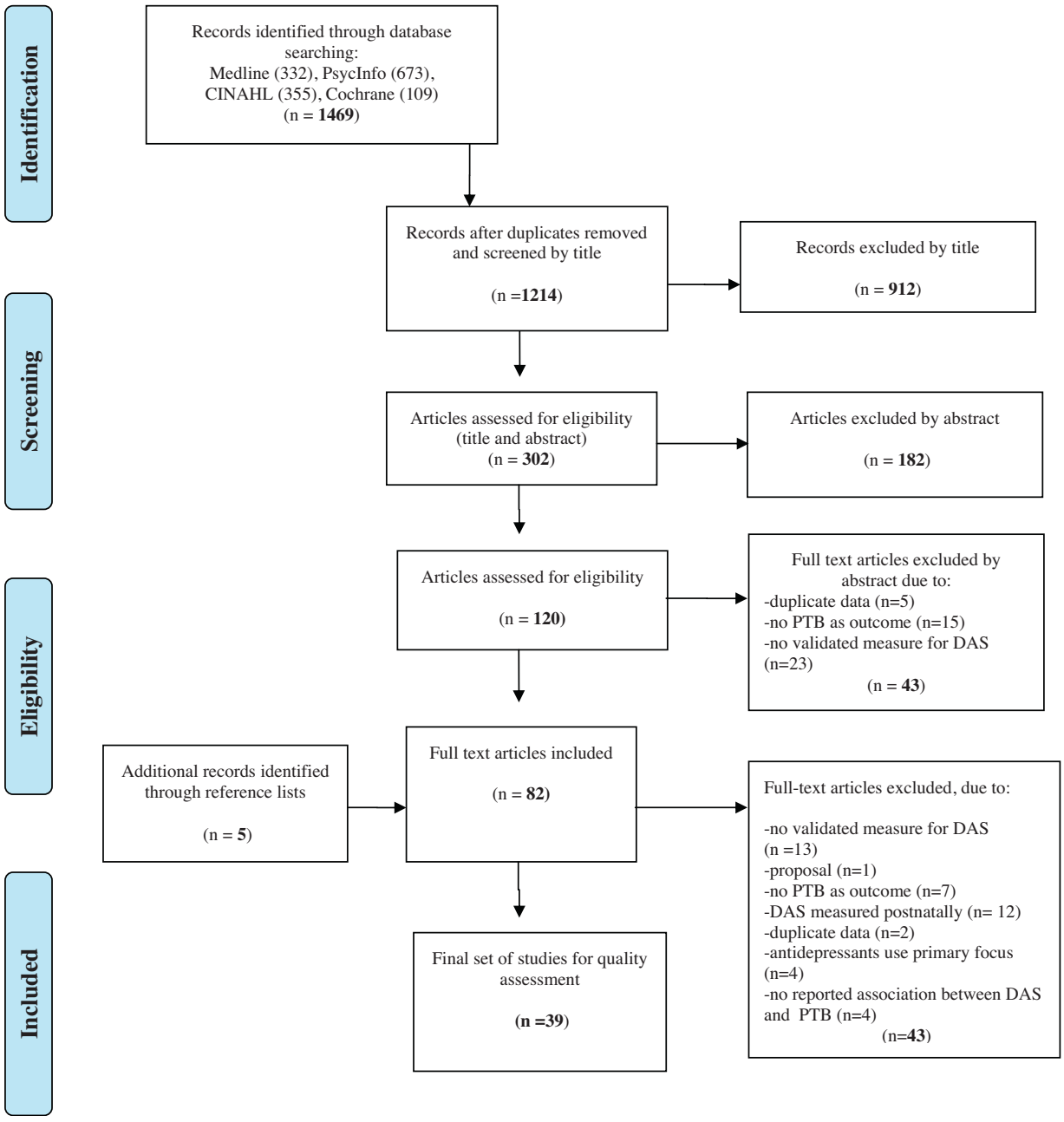

Fig. 1. Flow diagram for study selection.

3.3. Data synthesis

Individual studies were critically analysed, and the findings were subsequently summarised. The lack of homogeneity of data with respect to sample characteristics, methodology, assessment tools, timing and cut-off scores, diagnostic criteria and symptomatology, conceptualisations of exposure and definitions of PTB, was observed and precluded a meta-analysis.

3.4. Participant characteristics

Recruited participants were all pregnant women, ranging from those clinically diagnosed as depressed, to those experiencing various levels of depression, anxiety or stress symptomatology, and healthy comparison groups. While some studies controlled for age and its implications, most studies categorised women on that basis. Age range varied substantially across studies. Study variability was also present in ethnicity and race, socio-economic status, urban and rural settings and in the marital status, parity, education levels, and income of the participants. Black and Hispanic race and socioeconomically disadvantaged women with lower income and on public assistance were overrepresented across the studies. Some studies reported negative health behaviours pre- and during the pregnancy (e.g., smoking, drinking, abusing drugs, etc.) and controlled for behavioural practices and lifestyle as predictive of birth outcomes. However, the majority of studies did not assess participants' health behaviours.

3.5. Conceptualising preterm birth

Reported PTB rates ranged from 4.1% to 23% (mean = 9.1). Six studies reported the rates for PTB specifically for depressed (clinically diagnosed, and either on antidepressant medication or untreated) participants and these ranged from 8% to 32%

Table 3
Risk of bias among included studies.

First author (year) Country	Study design	Type of bias						Overall bias assessment
		Selection	Exposure assessment	Outcome assessment	Confounding factor	Analytical	Attrition	
Yonkers (2012) USA	Prospective cohort	Low	None	None	None	None	None	None
Copper (1996) USA	Prospective cohort	Low	Low	Low	Low	Low	Low	Low
Coussons-Reed (2012) USA	Prospective cohort	Low	Low	Low	Low	Low	Low	Low
Dayan (2002) France	Prospective cohort	Low	Moderate	Low	Low	Low	Low	Low
Fransson (2011) Sweden	Population-based	None	Low	Low	Low	Low	Cannot tell	Low
Glynn (2008) USA	Prospective cohort	Moderate	Low	Low	Low	Low	Low	Low
Hedegaard (1993) Denmark	Prospective population-based	Low	Moderate	Low	Low	Low	Low	Low
Ibanez (2012) France	Prospective cohort	Moderate	Moderate	Low	Low	Low	Low	Low
Kramer (2009) Canada	Prospective cohort	Low	Low	Low	Low	Low	Low	Low
Li (2000) USA	Population-based cohort	Moderate	None	Low	Low	None	None	Low
Lobel (2008) USA	Prospective cohort	Moderate	Low	Low	Low	Low	Moderate	Low
Mancuso (2004) USA	Prospective cohort	Moderate	Moderate	Low	Low	Low	Low	Low
Neggers (2006) USA	Prospective cohort	Moderate	Moderate	Low	Low	Low	Low	Low
Nordeng (2012) Norway	Population-based	None	Low	None	Low	Low	Low	Low
Nordentoft (1996) Denmark	Prospective cohort	Low	Moderate	Low	Moderate	Low	Low	Low
Orr (2007) USA	Prospective cohort	Low	Moderate	Low	Low	Low	Low	Low
Rini (1999) USA	Prospective Cohort	Moderate	Low	Low	Low	Low	Low	Low
Ruiz (2012) USA	Prospective Cohort	High	Low	Low	Low	None	Cannot tell	Low
Steer (1992) USA	Prospective cohort	Moderate	Low	None	None	Low	Cannot tell	Low
Wadhwa (1993) USA	Prospective cohort	High	Low	Low	None	Low	Low	Moderate
Andersson (2004) Sweden	Population-based	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Catov (2010) USA	Prospective cohort	Moderate	Moderate	Moderate	Low	Low	Low	Moderate
Dole (2003) USA	Prospective cohort	High	Moderate	Moderate	Low	Low	Moderate	Moderate
Faisal-Cury (2010) Brazil	Prospective cohort	Moderate	Moderate	Moderate	Low	Moderate	Low	Moderate
Gavin (2009) USA	Prospective cohort	Low	High	None	Moderate	Moderate	None	Moderate
Hoffman (2000) USA	Prospective cohort	Low	Moderate	Moderate	Moderate	High	Moderate	Moderate
Lau (2013) China	Prospective community based	Moderate	Low	Low	High	Moderate	Low	Moderate
Lobel (1992) USA	Prospective cohort	Moderate	Low	Moderate	Low	Low	Cannot tell	Moderate
Messer (2005) USA	Prospective cohort	Moderate	Moderate	Low	Low	Moderate	Cannot tell	Moderate
Orr (2002) USA	Prospective cohort	Moderate	Low	Low	Moderate	Moderate	Cannot tell	Moderate
Perkin (1993) UK	Prospective population	Low	Moderate	Moderate	Moderate	Low	Low	Moderate
Rondo (2003) Brazil	Prospective cohort	Moderate	High	Moderate	Moderate	Moderate	Low	Moderate
Smith (2010) USA	Prospective cohort	Moderate	Moderate	Low	Moderate	Low	Moderate	Moderate
Suri (2007) USA	Prospective naturalistic	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Wisner (2009) USA	Prospective cohort	Moderate	Moderate	High	Low	Moderate	High	Moderate
Bhagwanani (1997) USA	Prospective cohort	Moderate	Moderate	High	High	High	None	High

Table 3 (*Continued*)

First author (year) Country	Study design	Type of bias						Overall bias assessment
		Selection	Exposure assessment	Outcome assessment	Confounding factor	Analytical	Attrition	
Field (2005) USA	Prospective cohort	High	Low	Moderate	High	High	Cannot tell	High
Jesse (2003) USA	Prospective cohort	Moderate	High	Moderate	High	Moderate	Cannot tell	High
Straub (2012) USA	Prospective cohort	Moderate	Low	Moderate	High	High	Cannot tell	High

(mean = 15.5%). Sixteen studies defined prematurity beyond the generally accepted standard of birth before completing 37 weeks of gestation. Sub-categorisations included were by the type of preterm birth delivery (spontaneous or medically indicated), its timing (early vs. late), and by established causes (rupture of membranes or preterm labour). Despite the general consensus of using the categorical variable with a cut-off point of 37 weeks, a few studies explored gestational age length (in days and weeks) as well. One study defined PTB as birth before week 36,[2] another study before completed 35 weeks,[9] whereas another one[10] differentiated between a "clearly preterm" (<36 weeks) and "marginally preterm" (36–37 weeks). Two other adverse birth outcomes were commonly reported along with PTB – low birth weight (LBW) (babies, weighing less than 2500 g) and intrauterine growth restriction (IUGR) (baby weight that is below the 10th percentile for gestational age). However, it is important to differentiate amongst each one, because it is hypothesised that different adverse birth outcomes have different aetiology, although they may share overlapping risk factors and comorbid sequelae.

3.6. Types of exposure

In order to synthesise the findings and address the secondary aims of the review, studies were grouped by exposure (i.e., depression, anxiety and perceived stress or a combination thereof) and are reported in Tables 4.1–4.4 with studies ordered by level of bias.

3.6.1. Depression

Depression during pregnancy and its effect on PTB were explored in 14 studies. Estimates of the effect of depression on PTB in the studies which were assessed as having low risk of bias ranged from OR 1.13 to 3.93 and in general narrow confidence intervals were observed with the null value contained in only one of the studies,[11] where there was no clear link between major depressive episode and PTB. However, in the same study the authors found a significant increase in risk for PTB when depression was combined with the use of antidepressants (OR = 2.1 [95% 1.0–4.6]). Seven studies, assessed as having moderate/high risk of bias, estimated similar effects of OR 1.07–3.71. In four of them there was no statistical significance of the effect of DAS on PTB, as CI contained the null value. Overall, eight studies reported a significantly increased risk for PTB[8,12–18]; one study reported a positive predictive value between exposure and outcome,[19] and five studies reported no statistically significant increase in risk.[11,20–23] Both independent and mediated (through antidepressant use) effects for depression were identified across studies. A population-based study[8] noted that the risk for PTB increased with increasing severity of depression, suggesting a potential dose–effect interaction, whole another one[12] concluded that even moderate levels of depressive symptoms significantly elevated the risk for PTB. The use of antidepressants in combination with depression was strongly linked to prematurity in three studies.[11,22,23] Conclusions about the independent effect of depression versus depression with medication use, or medication use only with no clear signs of depression, remain conflicting. A robust study from Norway on over 63 000 women[14] identified that depression alone, rather than exposure to antidepressants during the pregnancy, was statistically significantly associated with a modest increased risk for PTB, while another smaller case-control study[22] of 90 women, grouped by (1) antidepressant use, (2) a diagnosis of depression alone, and (3) healthy controls, concluded that depression was predictive only when combined with the use of antidepressants. Furthermore, rates of PTB in the participants from the antidepressant use group were very high (14.3%), but none of the women diagnosed as depressed (no antidepressant use) had a premature birth. Similar effects were observed in the Yonkers et al.'s study[11] were again it was the use of antidepressants, rather than depressive symptomatology that presented an increased risk for PTB.

The most common tool used ($n = 6$) to measure depression in these studies was the Center of Epidemiological Studies-Depression CES-D, developed to measure depressive symptoms in the general population. It has been extensively validated and widely used in epidemiologic research and during pregnancy. In four of the studies, high levels of depressive symptoms measured were predictive of PTB, while in the other two studies the risk was not statistically significant. The Edinburg Postnatal Depression Scale was used in two studies, while the PRIME-MD, the Hopkins Symptom Checklist and the Beck Depression Inventory were used in one study each. All of the measures are widely used and validated in pregnancy populations. Of these four studies depressive symptoms were predictive of PTB.

In most of the studies ($n = 8$) assessment for depression was employed only once, usually during the second trimester measured on average at 20 weeks (range 10–36 weeks). In all studies with singular assessment a positive association between exposure and outcome was observed, whereas in studies that employed multiple assessment times (twice, three times or more) the predictive value of DAS was observed in only one (out of five) study.

Studies that used several tools ($n = 3$) in combination with a diagnostic clinical interview and thus reported on a clinical diagnosis of depression along with multiple assessment points during gestation[11,22,23] reported a statistically non-significant risk for prematurity. However, all depressed women in these studies were taking antidepressants (with the exception of Suri's study[22] subgroup of 30 non-users) and the effect of depression alone was difficult to differentiate, while the combination of both predicted PTB.

3.6.2. Anxiety

Anxiety in pregnancy was measured in four of the reviewed studies. Anxiety was a symptomatologically, rather than diagnostically, operationalised. It was significantly associated with PTB in

Table 4.1
Evaluation of studies (depression, $n = 14$).

Authors (year) Country	Sample size (n) Characteristics/setting	Measure of exposure/ symptoms or clinical diagnosis	Exposure assessment frequency (n), gestational week (x/40)	Outcome assessment		Significant measures of effect and associations RR/HR/OR [95%CI]	Adjusted for confounders	Risk of bias
				PTB type/rate	Other			
Yonkers et al. (2012) USA	2793 4 exposure groups (SRI and depression) 74% White 14% Hispanic 137 hospital-based clinics (2 states)	CIDI interview/ clinical diagnosis	$n = 2$, 17 and 28/40	E (4) L (14) S (10) MI (6) 8% PTB		OR* = 1.2 [0.68–2.1] *Major depression, no SRI OR** = 1.62 [1.0–2.5] **No major depression, SRI	Age, education, race, smoking, drug use, pregnancy history past depression, past psychiatric disorders	None
Fransson et al. (2011) Sweden	2904 Predominantly White National survey	EPDS/symptoms	$n = 1$, 16/40	S MI 5.3%		OR = 1.56 [1.03–2.35]	Age, civil status, residency status, education level, assisted conception, history of infertility	Low
Li et al. (2009) USA	791 Diverse race/ethnicity Urban Medical Care program	CES-D/symptoms in 41.2%	$n = 1$, 10/40 (6–18)	<37 9.3%	Miscarriage	HR = 1.9 [1.0–3.7]	Use of SSRI, age, smoking, education, race, gravidity, history of miscarriage, PTB or LBW	Low
Neggers et al. (2006) USA	3149 Predominantly Black Prenatal care clinic	CES-D/symptoms – psychological status	$n = 1$, 22–23/40	GA <37 GA <32 S MI 9.1% PTB (6.6% S)	LBW IUGR	OR= 1.3 [1.04–1.7]	Race, pre-pregnancy weight, previous PTD, parity, education, alcohol and tobacco use, history of hypertension, diabetes, gender of the infant	Low
Nordeng et al. (2012) Norway	63 395 Representative of population 50 out of 52 hospitals	Hopkins SC/ symptoms in 6.7%	$n = 2$, 17 and 30/40	<37 4.6%	Congenital malformation, LBW	OR = 1.13 [1.03–1.25]	SSRI, socio-demographics and lifestyle factors	Low
Ruiz et al. (2012) USA	470 Hispanics only Physician practices and community clinics	CES-D/"mild to severe" symptoms in 40.3%	$n = 1$, 22–24/40	E (9) L (24) S (28) MI (5) 7% (33) PTB		$\chi^2 = 5.33$, $p = .021$ *Interaction b/w depressive symptoms and hormones associated with PTB	History of PTB, preeclampsia, marital status, infections, age, BMI, GA for blood drawing	Low
Steer et al. (1992) USA	712 Minority groups (50% adolescents and 50% adults) 2 inner-city hospitals	BDI/symptoms (higher in adolescents)	$n = 1/28/40$	<37 9% in adults 12.4% in adolescents	LBW SGA	OR* = 3.39 [3.24–3.56] *In adults only (not predictive in adolescents)	Race, low BMI, inadequate weight gain, smoking, prior history of PTB, parity	Low
Gavin et al. (2009) USA	3019 65% White 25% Black 10% other Multi-centre POUCH study	CES-D/symptoms in 17%	$n = 1/15–22/40$	MI <35 MI 35–36 PTB <35 PTB 35–36/11% PTB (8% S; 3% MI)		OR = 1.1 [0.6–1.9]	Age, race, parity, Medicaid use, use of psychotropic medication	Moderate
Hoffman and Hatch (2000) USA	666 Lower SES 2 suburban rural sites	CES-D/symptoms in 28% (40% in low SES)	$n = 3$, 13, 28 and 36/ 40	<37 Not reported %	Foetal growth, GA	OR = 1.07 [0.87–1.31]	SES, social support, history of previous poor pregnancy outcome	Moderate
Orr et al. (2002) USA	1399 Only Black 4 hospital-based clinics	CES-D/symptoms	$n = 1$, 17/40	S PTB only 8.4% overall (12.7% in depressed)		RR= 1.96 [1.04–3.72]	Behavioural, clinical and demographic variables	Moderate

Table 4.1 (*Continued*)

Authors (year) Country	Sample size (*n*) Characteristics/setting	Measure of exposure/ symptoms or clinical diagnosis	Exposure assessment frequency (*n*), gestational week (*x*/40)	Outcome assessment		Significant measures of effect and associations RR/HR/OR [95%CI]	Adjusted for confounders	Risk of bias
				PTB type/rate	Other			
Smith et al. (2011) USA	1100 Hispanic (~50%) Black and White (~50%) 3 cohorts in Health Start Screening Initiative	PRIME-MD/ symptoms in 36%	*n* = 1/14–34/40	<37 8% in depressed	LBW SGA Complications of delivery Newborn status	OR = 1.83 [1.17–2.86]	Smoking, drug and alcohol use during pregnancy	Moderate
Suri et al. (2007) USA	90 3 exposure groups University setting	Structured clinical interview, HAM-D, BDI, PSS/symptoms and clinical diagnosis in 22–28%	Monthly assessments	<37 14.3% in antidepressant depressed group; 0% in depressed; 5.3% in no depression	GA, birth weight, Apgar scores, admission to NICU	OR* = 1.41 [0.26–7.73] *For antidepressant group	Age, parity, weight gain, medical risk factors	Moderate
Wisner et al. (2009) USA	238 3 exposure groups 2 hospital sites	SCID-ADS GAS SF-12 and interview/Cl diagnosis in 44.9%	*n* = 3, 20, 30 and 36/40	E and L 20% PTB in depressed and SSRI groups; 4–9% in the rest	Infant birth weight, neonatal characteristics	RR* = 3.71 [0.98–14.13] *Depression, no SSRI RR** = 5.43 [1.98–14.84] **SSRI exposure	Age and race maternal BMI	Moderate
Straub et al. (2012) USA	14 175 70% White 8% Black 13.7% Hispanic 19.4% on public assistance University hospital	EPDS/symptoms in 9.1%	*n* = 1, 24–28/40	4 strata: <37, <34, <32, <28 10.6% PTB (13.9% for depressed)	SGA LBW	OR = 1.3 [1.09–1.35]	Age, race, prior PTB, insurance status Multiple gestation	High

For abbreviations, see Table 4.4.

Table 4.2
Evaluation of studies (anxiety, $n = 4$).

Authors (year) Country	Sample size (n), characteristics/setting	Measure of exposure/ symptoms or clinical diagnosis	Exposure assessment frequency (n), gestational week (x/40)	Outcome assessment		Significant measures of effect and associations RR/HR/OR [95%CI]	Adjusted for confounders	Risk of bias
				PTB type/rate	Other			
Mancuso et al. (2004) USA	282 43% Black 32% Hispanic 24% White Urban prenatal clinics and private practices "Behavior in Pregnancy Study"	PSA/symptoms in Black women higher than in White Blood plasma hormonal analysis	$n = 3$, 18–20/40; 28–30/40; 35–36/40	<37 Not reported %	GA	$r = -19$ ($p < .01$)	Medical risk, parity, socioeconomic variables	Low
Orr et al. (2007) USA	1820 Predominantly Black 4 hospital-based clinics	PSEI/symptoms of increased anxiety in 28%	$n = 1$, 16/40	S only 7.4% S PTB		OR = 2.73 [1.03–7.23]	Smoking and drug use, BMI, history of PTB, Black race	Low
Catov et al. (2010) USA	667 30% Black Predominantly on public assistance Women's Hospital "Prenatal Exposure and Preeclampsia Prevention Study"	STAI/symptoms higher in Black women	$n = 1$, 18/40	<37 9.6% PTB	SGA	OR* = 1.48 [0.96–2.28] *For Black women	Age, education, smoking, marital status, BMI, preeclampsia	Moderate
Bhagwanani et al. (1997) USA	88 65% White 27% Black 8% Hispanic University Hospital	STAI/symptoms for A-T and A-S	$n = 2$, 8–28/40 and 6 weeks after	Non-defined 11% PTB	Anaemia, UTI, hypertension, GD, meconium presence, foetal distress, birth weight, Apgar, etc.	$p = .017$ High A-T scores correlated with PTB and increased risk was 5.6-fold; high A-S increased PTB risk 3-fold	Psychopathology	High

For abbreviations, see Table 4.4.

Table 4.3
Evaluation of studies (perceived stress, $n = 5$).

Authors (year) Country	Sample size (n), characteristics/setting	Measure of exposure/ symptoms or clinical diagnosis	Exposure assessment frequency (n), gestational week (x/40)	Outcome assessment		Significant measures of effect and associations RR/HR/OR [95%CI]	Adjusted for confounders	Risk of bias
				PTB type/ rate	Other			
Coussons-Read et al. (2012) USA	173 Hispanic 75% White 25% Medical Centre	NUPDQ DMHA Blood sample (inflammatory marker)/ symptoms	$n = 2$, 14–18/40; 28–32/40	<37 9.9%	GA	$R^{2\ adj} = .23$, $F(5159) = 11.369$, $p < .000$	Infection during pregnancy, combined effect of distress and inflammatory markers	Low
Hedegaard et al. (1993) Denmark	5459 Representative cohort Antenatal clinic in University Hospital	GHQ/symptoms	$n = 2$, 16 and 30/40	<37 3.5%		High stress later in pregnancy RR = 1.75 [1.20–2.54]	Age, smoking, educational level, parity, previous PTB, height and prepregnancy weight	Low
Nordentoft et al. (1996) Denmark	2432 Representative cohort Copenhagen University Hospital	Severity of Psychosocial Stressor Scale GHQ-12/symptoms	$n = 1$, 20/40	<37 8.7%	IUGR	OR = 1.14 [1.00–1.29]	Age, cohabitation with partner, education	Low
Lau (2013) China	584 Representative cohort Antenatal clinic in public hospital	PSS SF-12 Health Survey/ symptoms of increased stress in over 53%	$n = 1$, 18/40	<37 6.4%	LBW	OR = 2.45 [1.04–5.62]	Demographics, socio-economic, obstetrics, medical characteristics, smoking, alcohol, drug abuse	Moderate
Rondo et al. (2003) Brazil	865 Low income families 12 health units in 5 hospitals in Southeast Brazil	GHQ/symptoms of distress varied 22.1–52.9%	$n = 3$, 16; 20–26; and 30–36/40	<37 4.2%	LBW, IUGR	RR = 2.32 [1.18–4.60]	Age, education, marital status, income, parity, history of LBW, pre-pregnancy weight, height	Moderate

For abbreviations, see Table 4.4.

Table 4.4
Evaluation of studies (mixed exposure, $n = 16$).

Authors (year) Country	Sample size (n), characteristics/setting	Measure of exposure/ symptoms or clinical diagnosis	Exposure assessment frequency (n), gestational week (x/40)	Outcome assessment		Significant measures of effect and associations RR/HR/OR [95%CI]	Adjusted for confounders	Risk of bias
				PTB type/rate	Other			
Copper et al. (1996) USA	2593 63% Black 35% White 10 obstetric centres	STAI CES-D/symptoms of stress, anxiety and depression	$n = 1$, 25–29/40	S PTB at <35 weeks/3.9% And PTB <37/15.5%	IUGR LBW	High stress OR = 1.16 [1.05–1.29] Anxiety OR = 1.02 [0.99–1.06] Depression OR = 1.03 [0.99–1.06]	Age, marital status, insurance, education, tobacco, alcohol and drug use, Black race	Low
Dayan et al. (2002) France	634 Representative cohort Large University Hospital	STAI EPDS/symptoms of anxiety (not reported %) and high depression in 11.2%	$n = 1$, 20–28/40	<37 S 11.4%		Depression in underweight women OR = 6.9 [1.8–26.2] Anxiety in women with history of PTB OR = 4.8 [1.1–20.4]	Socio-demographics and biomedical factors	Low
Glynn et al. (2008) USA	415 48% White 23% Hispanic 14% Black 15% Other University Hospital in LA	PSS STAI P-SA/symptoms of perceived stress and anxiety	$n = 2$, 18–20 and 30–32/40	<37 9.1%	GA	Perceived stress OR = 3.08 [1.51–6.28] State anxiety OR = 2.49 [1.24–4.98]	Race, parity, smoking, gestation, medical risk	Low
Ibanez et al. (2012) France	1719 Middle to privileged class population 2 University maternal units	CES-D STAI/symptoms of anxiety in 7.9%; of depression 11.8%, and anxiety and depression in 13.2%	$n = 1$, 24–28/40	<37 S in 3.4% MI in 2.1% Overall PTB in 5.6%	GA, birth weight	Combined depression and anxiety for S PTB OR = 2.46 [1.22–4.94]	Age, education, parity, BMI, smoking, hypertension	Low
Kramer et al. (2009) Canada	5092 85% White 5% Black 10% Other Multicentre cohort study 4 study hospitals	DHS MSS; JSIS; ASSIS, PLES, PSS, S-ES LOT, CES-D biomarkers/ symptoms of anxiety and depression	$n = 1$, 24–26/40	S PTB <37 only 4.1%		Pregnancy-related anxiety OR = 1.7 [1.2–2.3]	Age, parity, living arrangement, birth place, smoking, education, income, height, BMI, medical/obstetric risk	Low
Lobel et al. (2008) USA	279 65% White 12% Black 12% Hispanic 10% Other University prenatal care facility	PDQ PLES STPI PRHS/symptoms of state anxiety, perceived stress and pregnancy-specific stress	$n = 3$, 10–25; 21–35/40 and 2 weeks after the last one	>37/not reported %	GA, birth weight	Pregnancy-specific stress (single factor combining stress and anxiety) ($B = -.18$, $p = .004$)	Obstetric and medical risk	Low
Rini et al. (1999) USA	230 53% Hispanic 47% White Medical Centre	Mastery Scale LOS S-ES STAI P-RA/symptoms of anxiety and stress	$n = 1$, 28–30/40	<37/not reported %	GA, birth weight	Prenatal stress OR = 1.59 $\beta = 0.46$, $p < .05$	Ethnicity, income, education	Low
Wadhwa et al. (1993) USA	90 77% White 13% Hispanic 7% Black Teaching Urban hospital	PSS, Hopkins SC P-RA DHS Schedule of life events/ symptoms of stress, pregnancy related anxiety	$n = 1$, 22–28/40	<37 13.2%	GA, Apgar scores, birth weight, intrapartum complication	Pregnancy-related anxiety* and PTB ($r = .25$, $p < .05$) Increase of 1 unit in anxiety, shortened gestation with 3 days *$p = .11$ when biomedical risk was controlled for	Age, parity, race, socio-economics, prenatal care, smoking	Low

Table 4.4 (*Continued*)

Authors (year) Country	Sample size (*n*), characteristics/setting	Measure of exposure/ symptoms or clinical diagnosis	Exposure assessment frequency (*n*), gestational week (*x*/40)	Outcome assessment		Significant measures of effect and associations RR/HR/OR [95%CI]	Adjusted for confounders	Risk of bias
				PTB type/rate	Other			
Andersson et al. (2004) Sweden	1465 Representative cohort 2 obstetric clinics in Sweden	PRIME-MD/clinical diagnosis of major depressive disorder (3.1%), dysthymia, GAD (5.9%); minor depressive disorder (7.1%), anxiety NOS (4.1%)	*n* = 1, 16–18/40	<37 S PTB 5.2% of PTB in diagnosed 2.5% of S PTB in diagnosed	SGA, respiratory distress asphyxia and malformation	Depressive disorder OR = 1.32 [0.68–2.56] Anxiety disorder OR = 0.90 [0.28–0.52]	Age, parity, marital status, employment, smoking, BMI	Moderate
Dole et al. (2003) USA	1962 Predominantly Black and low SES 2 perinatal clinics; The PIN study	Life experiences survey SSS/symptoms of depression, anxiety, and pregnancy-related anxiety and stress	*n* = 1, 24–30/40	S and MI <37 12%		Pregnancy-related anxiety and S PTB RR = 2.1 [1.5–3.0]	Smoking, alcohol, parity, poverty, bacterial vaginosis, medical problems	Moderate
Faisal-Cury et al. (2010) Brazil	831 Low SES Antenatal clinics in Sao Paolo	CIS-R/clinical diagnosis of depression and anxiety in 33.6%	*n* = 1, 20–30/40	<37 6.9%	LBW	OR = 1.03 [0.57–1.88]	Smoking, age and number of pregnancies	Moderate
Lobel et al. (1992) USA	130 Low SES women Predominantly Hispanic Public clinic	PSS STAI Medical risk Interviews/symptoms of perceived stress and state anxiety	*n* = 4 and 1 postnatal, 12.4 weeks at start with 10 days interval	Clearly preterm (<36) 4.6% Marginally preterm (36–37) 12.3%	Birth weight GA	Model of distress (perceived stress plus anxiety) significantly predicted PTB $r = -.23$ independent of medical risk In a regression analysis (not SEM) $r = .30$, $p < .03$)	Parity, number of life events, marital status, education, age, medical risk	Moderate
Messer, et al. (2005) USA	1908 59% White ~30% Black 30% low SES Prenatal care clinics; The PIN study	PI, LES CES-D WCQ/symptoms of depression and stress	*n* = 1, 24–29/40	<37 11.4%		High perceived stress and not intended pregnancy OR = 3.4 [2.6–4.5] High depression OR = 3.1 [2.4–3.9]	Age, education, race, marital status	Moderate
Perkin et al. (1993) UK	1515 White Teaching hospital in London	GHQ/symptoms of anxiety and depression	*n* = 3, at booking, 28, 36/40	PTB <36 weeks S Not reported %	Anaestesia Type of delivery	Anxiety OR = 0.99 [0.73–1.34] Depression OR = 1.28 [0.95–1.73]	35 socio-economic, psychological and personal; factors	Moderate
Field et al. (2006) USA	300 Depressed only women Prenatal clinic	CES-D SCID-interview STPI STAXI Cortisol/symptoms and clinical diagnoses for depression, symptoms for anxiety (state and trait)	*n* = 1, 20/40	<37 32%	GA, birth weight, birth length, head circumf.	Discriminant function of CES-D $\chi = .\mathbf{97}$, $p = .30$	Not reported	High
Jesse et al. (2003) USA	120 Predominantly White and low SES (~50% smoked) 3 Rural clinics	PPP, DHS SBI, S-ES 2 statements on depression AAS, PoP, LRB/symptoms of depression (~50%) and stress and abuse (15%)	*n* = 1, 16–28/40	<37 23%		Depression OR = 3.89 [1.18–12.73] Stress OR = 1.0 [0.9–1.2] Perception of pregnancy OR = 1.406 [1.02–1.94]		High

E, early PTB (<34 weeks); L, late PTB (<37 weeks); S, spontaneous delivery; MI, medically indicated; AAS, Abuse Assessment Screen; ASSIS, Arizona Social Support Interview Schedule; CIDI, World Mental Health Composite International Diagnostic Interview; CIS-R, clinical interview schedule revised, symptoms based; DHS, Daily Hassles Scale; GAS, Global Assessment Scale; HSC, Hopkins Symptoms Checklist; JSIS, Job-related Stress Intendedness Scale; LES, Life Experiences Survey; LOS, Life Orientation Scale; LOT, Life Orientation Test; LRB, Lifestyle Risk Behaviors; MSS, Marital Strain Scale; NUPDQ, Revised pregnancy specific distress questionnaire; PDQ, Prenatal Distress; PI, Pregnancy Intendedness; PLES, Prenatal Life Events Scale; PoP, Perceptions of Pregnancy; PPP, Prenatal Psychosocial Profile; P-RA, Pregnancy-related Anxiety; PRHS, Prenatal Health Behaviours Scale; PRIME-MD, Primary Care Evaluation of Mental Disorders; P-SA, Pregnancy-specific Anxiety; PSEI, Prenatal Social Environment Inventory; PSS, Perceived Stress Scale; SBI, Support Behaviors Inventory; SCID-ADS, Structured Clinical Interview for DSM-IV Atypical Depression Supplement; S-ES, Self-esteem Scale; SF-12, Health survey; SRLE, Schedule of Recent Life Events; SSS, Social Support Scale; STAI, State Trait Anxiety Inventory; STAXI, State Anger Expression Inventory; STPI, State-Trait Personality Inventory; WCQ, Ways of Coping Questionnaire.

three of the studies with estimates of effect ranging between OR 1.48 and 2.73. Two studies with a low risk of bias supported the significant role of anxiety in PTB. These studies used pregnancy-specific anxiety measures versus the general (state and trait, STAI) anxiety instruments. Assessing pregnancy-specific anxiety rather than state anxiety was associated with a better predictive model for prematurity.[24] Mancuso et al.[25] also explored the effect of biological markers of anxiety (corticotrophin-releasing hormones CRH) as predictive of PTB in 282 women, indicating that greater levels of maternal anxiety along with high levels of CRH were associated with shorter gestational age and PTB. Orr[24] reported a significant OR 2.73, with a wider CI. Catov et al.[26] studied 667 women and found significant associations between anxiety and gestational age and PTB only in Black women, who represented 30% of the sample; however, such association was not significant for White women. Women with anxiety had on average 3.3 days shorter gestations. Women with trait rather than state anxiety had a 5.6-fold increase in the risk for PTB.[27] Overall, women with increased anxiety had a significantly increased risk of spontaneous PTB.

The operationalisation of anxiety differed between studies, with some defining it as a relatively stable characteristic and an individual's general proneness to anxiety against the ability of being optimistic,[26] or as worries or concerns about health of the baby.[24] Other researchers defined anxiety as pregnancy-specific with particular feelings of panic or fear about the pregnancy.[25] In two of the four studies assessment was performed just once with three studies assessing anxiety after a minimum 16 weeks of gestation. Bhagwanani et al.[27] undertook initial assessments of anxiety across a wide range of gestation from 8 to 28 weeks, although it is unlikely that anxiety is a stable construct during this time. Two studies used the STAI which clearly differentiates between state and trait anxiety,[28] while pregnancy-specific anxiety was explicitly assessed through the Pregnancy-Specific Anxiety Scale[29] and pregnancy-specific items from the PSEI in full scale.[30]

3.6.3. Perceived stress

The effect of perceived stress on PTB was examined in five studies, which consistently demonstrated a statistically significant relationship. Of the three prospective studies, with low risk of bias, two demonstrated increased risk from OR 1.14 to RR 1.75. One study concluded that the combination of elevated distress and certain inflammatory processes was significantly predictive of PTB. Pregnancy-specific distress and elevated inflammatory markers were predictive of shortened gestational length and PTB.[31] The independent effect of stress was identified in one study,[32] while the rest reported a combination of elevated distress levels alongside inflammatory bio-markers, history of obstetric adversities, years of schooling, and smoking. The studies with moderate risk of bias, demonstrated a larger estimate of the effect of perceived stress on PTB, and wider-ranging CIs.

Perceived stress was assessed between one and three times across the studies at a minimum of 14 weeks gestation. Levels of stress, measured during the 2nd and 3rd trimesters were identified as best predictors of prematurity.[31–33] In Hedegaard et al.'s study,[32] it was stress experienced during week 30, and not earlier (at 16 weeks), that contributed to an increased PTB risk. The General Health Questionnaire (GHQ and GHQ-12 forms) was used in three of the studies as a measure of stress. The GHQ is a screening instrument used to detect the presence of minor psychiatric morbidity in patient and community samples. It relies on assessing psychological and psychosocial symptoms, such as somatic symptoms of anxiety, stress, social dysfunction, insomnia and severe depression. Other tools were the Denver Maternal Health Assessment, DMHA, which measures overall maternal stress through a combination of daily stress experiences and life events through the focus of perceived-self efficacy, and the Severity of Psychosocial Stressor Scale, combined with selected items from the DSM-IV-TR diagnostic criteria for anxiety.[34]

3.6.4. Mixed exposure (DAS)

The majority of studies ($n = 16$) explored a variety of potential psychological risk factors simultaneously. Overall, 13 of these studies reported a significant increase in the risk for PTB for women experiencing DAS during pregnancy.[9,10,35–45] Three studies[46–48] used diagnostic criteria for major depressive disorder and generalised anxiety disorder to clearly differentiate between symptoms and syndromes. PTB rates in the diagnosed participants ranged from 5.2% to 32%, however, with no statistically significant effect size.

Estimates of the effect of exposure on PTB in the studies, which were assessed as having low risk of bias ($n = 8$) ranged from OR 0.90 to 6.9 with most studies reporting narrow CIs, and three of these reporting on a non-significant risk for PTB.[2,46,47] Within all low bias studies, in the majority ($n = 6$) assessment was performed once – usually during the second trimester of gestation (16–28 weeks) employing multiple measures, and all were predictive of increased risk for PTB.

Ibanez et al.[39] identified the combination of depressive and anxiety symptoms to be the worst condition during pregnancy and the best predictor for adversity and PTB compared with the independent risk of depression or anxiety. Interestingly, Perkin et al.[2] found no increase in the risk for PTB in women experiencing depression or anxiety during pregnancy. The cut-off time-frame that they specified as PTB was birth at less than 36 weeks gestation, thus potentially missing out on the women who gave birth between 36 and 37 weeks. Furthermore, this study employed the GHQ-12 tool in their assessment of psychological distress, which has been deemed unsuitable for use in pregnancy due to confounding in its scoring methods in a study on pregnant women experiencing pre-labour rapture of membranes at term.[50]

Generally, in seven studies the increase in risk was independent of DAS, after controlling for major confounders including Black race and biomedical problems, while in the rest of studies ($n = 9$) the effect was mediated through high levels of cortisol, medical risks, and smoking.

The multidimensional framework, defined by Lobel[51] as *pregnancy-specific distress*, was used in five studies.[10,38,42,44,45] They were all assessed as low in bias and all provided evidence of a precise effect of the association between DAS and PTB.

For all 39 studies in this review, assessment of DAS was performed by self-report questionnaires ($n = 36$) and only in few studies a diagnostic interview was used, either on its own or in combination with a self-report instrument. Thus, whether psychological mood was at a diagnostic level for clinical disorder or at subclinical level and how these determined birth outcome, was hard to interpret. In 14 studies, measures were employed more than once. A wide distribution of assessment points discourages interpretations about when is the best time to assess DAS throughout the pregnancy; however, higher levels of DAS experienced during the third trimester were best predictive of PTB and shortened gestational length.

3.6.5. Risk factors and confounders

Studies varied greatly in the inclusion of risk factors and potential confounders. Most studies included at least the established minimum by the general PTB literature for confounders, such as age, socio-economic status, race/ethnicity (predominantly Black and Hispanic), education level, parity, a history of PTB, and smoking and/or substance abuse, with the exception of two studies[27,40] that did not report on any. Other risk factors and

confounders that have emerged in recent research included domestic violence, the use of SSRI and antidepressants pre- and during the pregnancy, body mass index (pre- and during pregnancy), chronic medical conditions such as diabetes, asthma or cardio-vascular disease, personality factors and resources, social support and living arrangements.[52,53] A significant effect on the relationship between DAS and PTB was the use of antidepressants, existing medical conditions, and infections during pregnancy.

The distinction between risk factors and confounders was not made clear in most studies, with the exception of the studies that employed multilevel modelling and had conducted a stratified analysis prior to model testing, where confounders are robustly identified and then successfully controlled for.

4. Discussion

This review explored the association between DAS and PTB. In summary, 26 out of 39 studies provided Level III-2 evidence and of these, 19 were assessed to have low risk of bias. Thus, findings suggest an increased overall risk for prematurity when a woman experiences one or more of the described psychological disorders. Furthermore, apart from a full clinical diagnosis of a disorder, a sub-clinical or symptomatological manifestation alone is found to be also predictive of PTB, and this has important clinical and practical implications. Pregnancy-specific distress, identified as a combination of pregnancy-specific anxiety and worries, and elevated perceptions of stress, is also a powerful predictive concept when exploring psychosocial determinants of PTB.

Considering all the studies, regardless of level of bias, PTB was significantly and independently predicted by depression, anxiety, or perceived stress (or in any combination between these) in 15 studies. Whenever the type of prematurity was specified, it was spontaneous rather than medically indicated PTB that was predicted by DAS. In the rest of the studies ($n = 24$), this association was moderated and mediated by various confounding variables, with medical risks and smoking, the most consistently identified. Health habits, in the form of lifestyle and healthy choices, the use of antidepressants, and past psychiatric disorders were also mediating variables.

In terms of socio-cultural factors, the findings suggest that race/ethnicity as well as low socio-economic status were related to several other variables that influence PTB, such as self-care, smoking, drug and alcohol abuse, and accessing adequate antenatal care. Specifically, the association of ethnicity to PTB was mediated through lower levels of personal resources, language barriers, economic difficulties, separation from friends and family, racial and neighbourhood discrimination for migrants,[19,31,44] which all present an important area for future investigations. This finding is in line with the literature that explores Black race as one of the most predictive factors for PTB.[54–56]

In 14 studies, women were assessed on psychological measures more than once and repeated perinatal screening suggests an appreciation that mental health status during pregnancy is not static. It can be argued that measuring depression in early pregnancy may not be an accurate predictor because the development of subsequent depression might go undetected. A strong confounder of the effect of depression on PTB is the use of antidepressants during pregnancy and their moderating effect, which has rarely been explored independently, with few exceptions.[11,22] It is possible that the level of clinical depression could potentially moderate this pathway, either directly or through the antidepressants required for more severe depression.

While there seems to be a general agreement on operationalising antenatal depression, it is important to note that there are various ways of conceptualising both anxiety and stress, and in most studies these terms have been used concurrently. This lack of differentiation carries important implications on the specificity of the type of assessment either as a cluster of symptoms or a clinical disorder. Furthermore, during pregnancy anxiety was reported to have a medium-to-large correlation with depressive symptoms.[57] This review highlights the importance of using a clearly defined multidimensional approach in the operationalisation of pregnancy-specific distress, encompassing both anxiety and perceived stress related to pregnancy, such as that proposed by Lobel[51] which provides a definitive and inclusive approach to understanding pregnancy-specific distress and its precise effect. In a review[58] on pregnancy-specific stress measures where 15 tools were identified and their psychometric properties examined, it was suggested that pregnancy-specific stress is: (1) associated, but not identical to general stress, and (2) pregnancy-specific stress was indeed predictive of PTB. It also is concluded that a multidimensional theoretical concept should be applied in measuring distress during pregnancy. Likewise, it is critical to be as descriptive and specific as possible in the operationalisation of PTB.

While existing reviews[1,59,60] explore the relationship between various adverse psychological states during the pregnancy and poor birth outcomes, this review is the first, to our knowledge, to focus comprehensively on three of the most common psychological disorders during pregnancy, and their association with PTB, specifically. Although Alder et al.[59] concluded that women experiencing depression and anxiety in general had more pregnancy and birth complications, the findings of that review missed the differentiation between clinical and sub-clinical depression and anxiety. While in the current review most results are based on assessing symptoms via research-based measures, an overall finding is that even moderate levels of sub-clinical mood disorders increases the risk for adverse birth outcome. Importantly, this review adds to the understanding of antenatal assessment of symptoms versus syndromes. In order to be able to predict potential adverse birth outcomes, women who are pregnant and present with depression or anxiety symptoms rather than a full clinical diagnosis for the above, deserve careful evaluation and monitoring along with exploration of added risk factors.

5. Conclusion and clinical implications

Health practitioners engaged in providing perinatal care to women, such as obstetricians, midwives, nurses, and mental health specialists should be aware of the association between antenatal DAS and the risks for PTB. Prevention should include various approaches to identify and address maternal psychological needs, as fully as any medical/physiological aspects of antenatal care. Understanding the associated risks for PTB in women experiencing DAS during pregnancy is essential in a clinical setting, particularly in planning effective strategies to manage mental health during the perinatal period and thus reducing the psychological impact of potential prematurity. Importantly, the results from this review conclude that until there is a better common understanding of the concepts measured perinatally, it is hard to specify an appropriate way to intervene, heightening the need for further research, better operationalisation of perinatal moods, and standardised measures of both predictor and outcome variables.

Conflict of interest

The authors have no conflicts of interest to disclose.

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