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REVIEW ARTICLE

The association between maternal cortisol and depression during pregnancy, a systematic review

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Abstract Timing of cortisol collection during pregnancy is an important factor within studies reporting on the association between maternal cortisol and depression during pregnancy. Our objective was to further examine the extent to which reported associations differed across studies according to time of maternal cortisol collection during pregnancy. On December 15, 2016, records were identified using PubMed/MEDLINE (National Library of Medicine), EMBASE (Elsevier; 1974–), Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO), PsycINFO (EBSCO), and Web of Science Core Collection (Thomson Reuters). Unique abstracts were screened using the following inclusion criteria: (1) maternal cortisol assessed during pregnancy; (2) antepartum depression assessed during pregnancy using a screening instrument; (3) reports on the association between maternal cortisol and antepartum depression; (4) provides information on timing of cortisol assessment during pregnancy, including time of day and gestation; and (5) not a review article or a case study. One thousand three hundred seventy-five records were identified, resulting in 826 unique abstracts. Twenty-nine articles met all inclusion criteria. On balance, most studies reported no association between maternal cortisol and antepartum depression (N = 17), and saliva and blood were the most common reported matrices. Morning and second and third trimesters were the most common times of collection during pregnancy. Among studies reporting an association (N = 12), second-trimester and third-trimester cortisol assessments more consistently reported an association and elevated cortisol concentrations were observed in expected recovery periods. Our review adds to the existing literature on the topic, highlighting gaps and strategic next steps.

Keywords Antenatal · Cortisol · Depression · Perinatal · Pregnancy

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Background

Depression during pregnancy, defined hereafter as antepartum depression, is highly prevalent, affecting approximately 20–25% of pregnant women globally (Gavin et al. 2005; Gelaye et al. 2016). Antepartum depression can have devastating affects for both the mother and infant and is linked to a number of adverse health-related behaviors and outcomes. Such behaviors and outcomes include poor maternal nutrition (Barker et al. 2013), increased substance use (Horrigan et al. 2000), preeclampsia (Kurki et al. 2000), spontaneous preterm delivery (Orr et al. 2002), postpartum depression (Dietz et al. 2007), and impaired fetal and infant growth (Rahman et al. 2004; Hoffman and Hatch 2000). Estimates for the increase in risk for certain outcomes are as high as 39% for preterm birth, 45% for intrauterine growth restriction, and 49% for low birth

weight delivery (Grote et al. 2010). Based on such findings, the American College of Obstetricians and Gynecologists (ACOG) now recommends that clinicians screen for depression at least once during the perinatal period, and an understanding of the underlying neurobiological pathways continues to be an important research objective.

One such candidate pathway is the hypothalamic pituitary adrenal (HPA) axis (Pariante and Lightman 2008; Penninx et al. 2013; Knorr et al. 2010; Stetler and Miller 2011; Kino 2015). The HPA axis is one of the body's stress-response systems and plays a crucial role in homeostatic regulation. Pregnancy is a period of profound physiological changes during which increases in maternal and placental corticotrophin-releasing hormone increase circulating maternal cortisol levels (Brunton et al. 2008; Lachelin 2013; Burke and Roulet 1970; Kirschbaum et al. 2009). Such naturally occurring adaptions are thought to occur to aid in fetal lung maturation (Ballard and Ballard 1972) and fetal growth (Bolten et al. 2011) and to prime the placenta for childbirth (Sandman et al. 2006). Saliva, blood, and urine are biological matrices commonly used to assess cortisol levels during pregnancy and reflect cortisol levels in the past 1 to 24 h. Using such matrices, cortisol has been observed to follow a diurnal trend with peak levels at awakening and nadir levels in the evening. Differences in peak and nadir cortisol levels have also been observed to widen as pregnancy progresses (Brunton et al. 2008). In order to assess long-term cortisol secretions reflecting the past 1 to 3 months, hair has emerged as another matrix of choice (Wosu et al. 2013). A commonly cited concern of hair is cortisol degradation due to prolonged environmental exposure (Dettenborn et al. 2012). Given such differences in the time windows these matrices represent, reviews of the literature for the association between maternal cortisol and antepartum depression can be increasingly complicated.

Previous findings for the association between maternal cortisol levels and antepartum depression have been mixed. When evaluating maternal cortisol concentrations (basal or in response to awakening or stressful stimuli), some investigators report statistically significant differences comparing pregnant women with and without depression (Bjelanovic et al. 2015; Diego et al. 2009; Field et al. 2009; Hoffman et al. 2016; Lommatzsch et al. 2006; Murphy et al. 2015; O'Connor et al. 2014; O'Keane et al. 2011; Parcells 2010; Peer et al. 2013; Voegtline et al. 2013). However, a number of investigators have reported no such differences (Braithwaite et al. 2016; Davis et al. 2007; Deligiannidis et al. 2013; Evans et al. 2008; Glynn and Sandman 2014; Goedhart et al. 2010; Hellgren et al. 2013; Iliadis et al. 2015; Kaasen et al. 2012; Katz et al. 2012; Luiza et al. 2015; Monk et al. 2011; Pluess et al. 2010; Rouse and Goodman 2014; Salacz et al. 2012; Shaikh et al. 2011; Wikenius et al. 2016; Deligiannidis et al. 2016). Reasons for such inconsistencies may be due to differences in methodologies across studies, such as differences in the timing and method of maternal cortisol assessment. Recent reviews on the association between maternal cortisol levels and antepartum depression conclude that pregnant women with antepartum depression present with elevated cortisol concentrations and blunted awakening responses when compared to non-depressed pregnant women (Seth et al. 2016; Serati et al. 2016; Iliadis et al. 2015). However, the role of cortisol collection method and timing of assessment during pregnancy requires additional investigation. Therefore, the objective of this systematic review was to further examine the extent to which reported associations between maternal cortisol levels and antepartum depression differed across studies according to timing of cortisol collection, thereby building upon the work of previous reviews on the topic.

Methods

Studies evaluating the relationship between maternal cortisol and antepartum depression were identified by searching PubMed/MEDLINE (National Library of Medicine), EMBASE (Elsevier; 1974–), Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO), PsycINFO (EBSCO), and Web of Science Core Collection (Thomson Reuters) from inception through December 15, 2016. Controlled vocabulary terms (e.g., MeSH or Emtree terms) were included when available and appropriate. The search strategies were designed and executed by a librarian (PAB). No language limits or year restrictions were applied, and bibliographies of relevant articles were reviewed to identify additional studies. The exact search terms used for each of the databases are provided in the supplementary document.

Records were identified through databases, and duplicates were removed. The abstracts of the remaining records were screened for inclusion using the following eligibility criteria: (1) maternal cortisol assessed during pregnancy; (2) antepartum depression assessed during pregnancy using a screening instrument; (3) reports on the association between maternal cortisol and antepartum depression; (4) provides information on timing of cortisol assessment during pregnancy, including time of day and gestation; and (5) not a review article or a case study. We did not restrict inclusion according to depression screener; however, studies that did not report a depression screener or assessed "blues" or stress more generally were excluded. Findings from all studies were reported, and reported p values ≤ 0.05 were deemed statistically significant.

Results

One thousand three hundred seventy-five records were retrieved from the database search, resulting in 826 unique records for screening. Twenty-seven studies met all inclusion

criteria, and a scan of the references of these studies resulted in two additional studies that also met all inclusion criteria. In total, 29 studies were included in our systematic review (Fig. 1). The majority of the screened studies failed to meet inclusion because investigators reported on the association between maternal cortisol and infant outcomes (or between maternal depression with infant outcomes), rather than on the association between maternal cortisol and antepartum depression (N = 774 out of 826, 93.7%). Table 1 provides a description of each of the 29 studies; 12 reported a statically significant association between maternal cortisol and antepartum depression (Bjelanovic et al. 2015; Diego et al. 2009; Evans et al. 2008; Field et al. 2009; Hoffman et al. 2016; Lommatzsch et al. 2006; Meliska et al. 2013; Monk et al. 2011; O'Connor et al. 2014; O'Keane et al. 2011; Peer et al. 2013; Voegtline et al. 2013), and 17 studies did not (Braithwaite et al. 2016; Davis et al. 2007; Deligiannidis et al. 2016; Glynn and Sandman 2014; Goedhart et al. 2010; Hellgren et al. 2013; Iliadis et al. 2015; Kaasen et al. 2012; Katz et al. 2012; Luiza et al. 2015; Pedersen et al. 1993; Pluess et al. 2010; Rouse and Goodman 2014; Salacz et al. 2012; Shea et al. 2007; Susman et al. 1999; Wikenius et al. 2016).

Study design characteristics of eligible studies

Among the 29 studies, publication dates ranged from 1993 to 2016 and study populations were based exclusively in European or North American countries. The majority of studies sampled study participants from clinical settings (N = 18). Total sample sizes ranged from 29 (Meliska et al. 2013) to 2810 (Goedhart et al. 2010), and reported mean ages ranged from 17 to 37 years. The most common depression screeners reported were the Edinburgh Postnatal Depression Scale followed by the Center for Epidemiologic Studies Depression Scale. The most common matrix reported for the determination of maternal cortisol levels was saliva (N = 14), followed by blood (plasma (N = 4) and serum (N = 3)), urine (N = 3), and hair (N = 2). Two studies used both urine and plasma (Luiza et al. 2015; Pedersen et al. 1993), and one study used both saliva and serum (Kaasen et al. 2012). Among the studies using saliva, blood, and urine, morning collections were most common (8:00 a.m.–11:30 a.m.). Some studies reported multiple collections of maternal cortisol throughout the pregnancy period (N = 18 studies). However, such studies were predominately restricted to

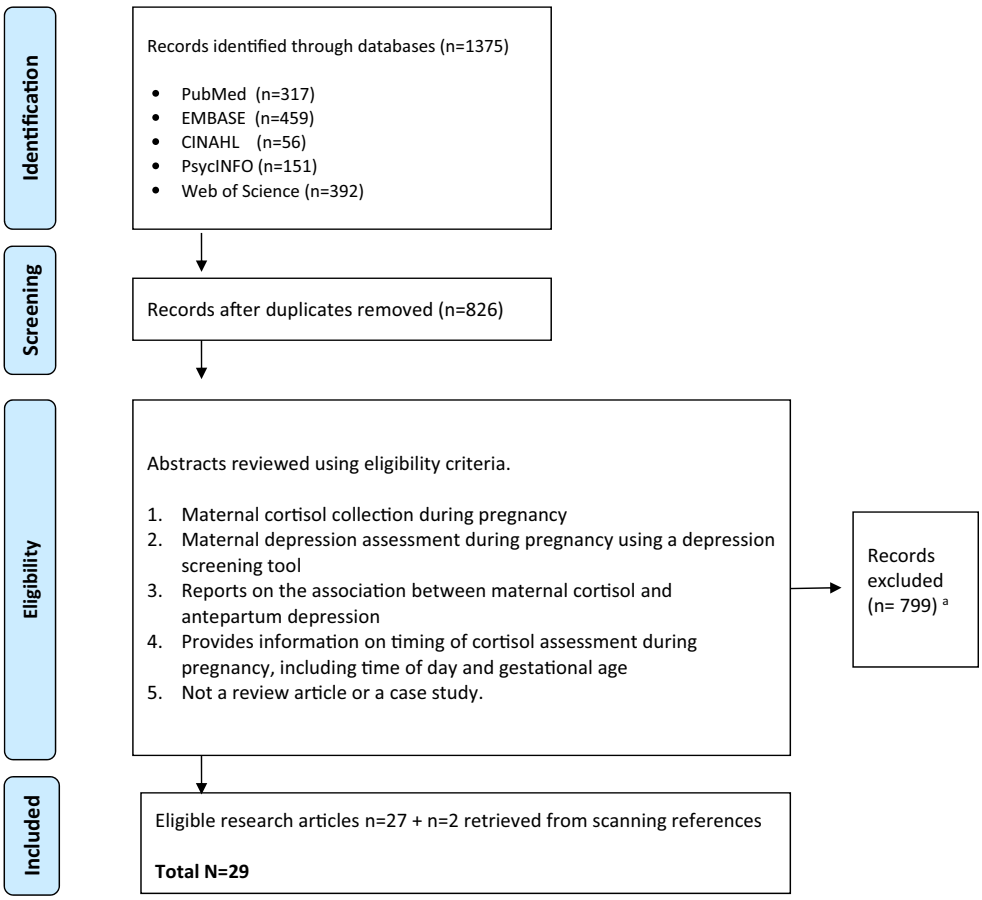

Fig. 1 Flow diagram of selection process. *Superscript letter a* denotes reasons for exclusions: does not report on the association between cortisol during pregnancy and depression during pregnancy (n = 774), a review article on the topic (n = 6), reports on the association between cortisol during pregnancy and depression during pregnancy but depression instrument either not mentioned or not compatible with criteria (n = 10), missing important information on time of depression and cortisol collection during pregnancy (n = 4), and met inclusion criteria but not a full article (n = 5)

Table 1 Findings on the association between cortisol and depression during pregnancy from studies meeting all inclusion criteria

#	First Author, Year	Country (Recruitment)	Total N (Age) [#Depressed During Pregnancy]	Depression Instrument (Time during pregnancy)	Cortisol matrix (Time during pregnancy) [Single or multiple samples] Method of analysis	Association between antepartum depression and maternal cortisol levels during pregnancy
1	(Bjelanovic et al., 2015)	Bosnia and Herzegovina (Clinic – Hospitalized)	N=180 (18-40y) [#DEP=UNCLEAR]	BDI-I (Third trimester)	Saliva (Third trimester; 8am and 5pm) [Multiple samples] ELISA	Elevated cortisol associated with depression at 8am (r=0.239, p=0.001) and 5pm (r=0.206, p=0.005)
2	(Braithwaite et al., 2016)	UK (Unclear)	N=103 (18y+) [#DEP=24]	EPDS (cutoff 10) (Second or third trimester)	Saliva (Second or third trimester; between 1-7pm) [Multiple samples] ELISA	No effect of group (depression status) (ANOVA F = 0.646, p = 0.430), or group by time (trimester) interactions (F = 3.724, p =0.203), suggesting no change in salivary cortisol across the test session in response to film
3	(Davis et al., 2007)	USA (Clinic)	N=247 (18-43y) [#DEP=13-18%]	CES-D (3 times during pregnancy: 18-20, 24-26, and 30-32 wGA)	Saliva (3 times during pregnancy: 18-20, 24-26, and 30-32 wGA; mean time 2:20pm) [Multiple samples] RIA	Depression was not correlated with measures of maternal cortisol, "all correlation coefficients were less than 0.1 and not statistically significant".
4	(Deligiannidis et al., 2016)	USA (Unclear)	N=44 (18-40y) [#DEP=24]	EPDS (cutoff 10) (28-33w GA)	Saliva (28-33w GA; Between 11am-5pm) [Multiple samples] ELISA	There was no correlation between EPDS score and baseline cortisol (r=0.141, p ='not statistically significant'). The average cortisol values at each of the six TSST time points and longitudinal changes did not differ comparing depressed and healthy comparison groups.
5	(Diego et al., 2009)	USA (Clinic)	N=80 (18-39y; Mean=27y) [#DEP=40]	CES-D + SCID (18-20w GA)	Urine (18-20w GA; mid-morning) [Single sample] RIA	Depressed women had elevated cortisol levels compared to non-depressed women. Prenatal cortisol levels also correlated with CES-D scores (r= 0.37, p<0.01)
6	(Evans et al., 2008)	USA (Clinic)	N=182 (18-40y) [#DEP=16; #DEP+ Anxiety=9]	CESD + SCID (Second trimester and between 33-39w GA)	Saliva (33-39w GA; Between 10:30-11:30am) [Multiple samples, 3 times] RIA	Morning cortisol from depressed pregnant women did not differ from controls (p-value >0.99), however, cortisol concentrations were elevated comparing comorbid pregnant women (anxiety and depression) to controls (p=0.006)
7	(Field et al., 2009)	USA (Clinic)	N=336 (Mean=25y) [#DEP=131]	CES-D (cutoff 16) + SCID (20 and 32w GA)	Urine (20 and 32w GA; First morning) [Multiple samples] HPLC	Only at 32w GA, cortisol levels among depressed women were significantly higher than non-depressed women (71.7 units vs. 10.5 units, p-value= 0.01)
8	(Glynn and Sandman, 2014)	USA (Clinic)	N=170 (Mean=30y) [#DEP=34]	CES-D (14-16, 24-26, 36+w GA)	Plasma (14-16, 24-26, 36+w GA; afternoon) [Multiple samples] ELISA	Prepartum cortisol was not associated with depressive symptoms at 3 or 6 months (partial correlation coefficients ranged from -0.10 to 0.08, p-values > 0.05).
9	(Goedhart et al., 2010)	UK (Community)	N=2810 (Mean=31y) [#DEP=1384 low, 1123 moderate, 287 high]	CES-D (First trimester)	Serum (6-20w GA; 8-9am) [Single sample] RIA	Women with the highest depressive symptoms had higher median cortisol levels compared to women with moderate and low depressive symptoms, however the elevation was not statistically significant (425.9, 425.5, and 417.9 respectively, p-value=0.366).

Table 1 (continued)

10	(Hellgren et al., 2013)	Sweden (Community)	N=134 (Mean= 31-39y) [#DEP=57 never, 39 previously, 38 current]	EPDS (cutoff 13) (17 and 32w GA) and MINI (35-39 wGA)	Saliva (35-39w GA) [Multiple samples, Waking+15'+30'+45'] Cobas Elecsys Kit	No main effect of group (depression status) was found (F(2,136) = 0.67; p = 0.515). No group by time interaction was found (F(6,346) = 0.46; p = 0.835). Results remained unchanged when age, educational level, and treatment were added as covariates.
11	(Hoffman et al., 2016)	USA (Clinic)	N=92 (18-45y) [#DEP=Unclear]	CES-D (5 time points: 16, 22, 28, 34, and 40w GA)	Hair (3cm at 16w, 28w, 40w GA; representative of each trimester) [Multiple samples, 3 times] ELISA	Significant relationships were observed for: 1) first trimester cortisol and depression scores in week 40 (r=0.27, p=0.02), 2) second trimester cortisol and depression at week 16 (r=0.32, p=0.002) and week 28 (r=0.25, p=0.02), and 3) third trimester cortisol with depression at week 16 (r=0.27, p=0.01) and week 28 (r=0.24, p=0.03).
12	(Iliadis et al., 2015)	Sweden (Community)	N=268 (18+y) [#DEP=49]	EPDS (cutoff 13) (36w GA)	Saliva (36w GA; between 8-10pm) [Single sample] ELISA	No significant correlation was observed between cortisol levels in pregnancy week 36 and EPDS scores in late pregnancy and postpartum. However, an association was observed between postpartum salivary cortisol and postpartum depression (adjusted Odds Ratio = 4.5; 95% Confidence Interval: 1.5–14.1)
13	(Kaasen et al., 2012)	Denmark (Clinical)	N=126 (19-43y) [#DEP=55]	EPDS (cutoff 13) (18-22 wGA)	Saliva (12-38w GA; Between 9-10pm) Serum (12-38w GA; Between 8-9am) [Single sample of each] Both used RIA	When comparing non-depressed and depressed, no difference in unadjusted (3.1 units vs. 3.5 units, p=0.58) or adjusted (3.2 vs. 2.8, p=0.56) mean evening salivary cortisol. Similarly, no difference in unadjusted (0.4 units vs. 0.4 units, p=0.65) or adjusted (0.4 vs. 0.4, p=0.99) mean morning serum cortisol
14	(Katz et al., 2012)	USA (Community and Clinic)	N=106 (Mean=33y) [#DEP=74]	BDI-I (cutoff 15) + SCID (<24w GA)	Plasma (<24w GA; 9-11h, 11-16h, 16-19h) [Multiple samples] RIA	Mixed model analyses demonstrated a significant effect of trimester on total cortisol levels (F=11.2 ; df=3,7 ; p<0.005), but no main effect of depression nor any interaction between trimester and depression
15	(Luiza et al., 2015)	USA (Clinic)	N=50 (Mean=22y) [#DEP=25]	EPDS (cutoff 11) (First trimester, Mean 11.2 w GA)	Plasma and urine (6-16w GA; morning) [Single sample of each] ELISA	Neither plasma cortisol nor the urine cortisol/creatinine ratio were significantly different comparing depressed and non-depressed pregnant women (plasma: 30.6 vs. 31.5 ng/ml; urine cortisol/creatinine ratio: 0.71 vs. 0.99; p-values not mentioned)
16	(Lommatzsch et al., 2006)	Germany (Community)	N=40 (20-40y) [#DEP=16]	EPDS (cutoff 9) (30 and 37w GA)	Serum (30 and 37w GA; Between 3-7pm) [Single sample] ELISA	There were significantly higher cortisol levels comparing depressed pregnant women (median: 620nmol/L) to non-depressed pregnant women (median: 392 nmol/L; p <0.01). However positive correlation of EPDS scores and cortisol did not reach statistical significance (data not shown).
17	(Meliska et al., 2013)	USA (Community)	N=29 (Mean=26y) [#DEP=19]	HRSD (cutoff of 14) (<34 w GA)	Serum (<34 wGA; Evening, 6pm-11am Every 30 minutes) [Multiple samples] Solid Phase RIA	HRSD scores were positively correlated with cortisol among the depressed (r = 0.592, p = .012), but not among healthy controls (r= 0.074, p=0.819)
18	(Monk et al., 2011)	USA (Clinic)	N=97 (18-40y) [#DEP=7 #DEP+Anxiety=12 #Anxiety only=17 #Controls=61]	SCID (Second trimester and 36-38w GA)	Saliva (36-38 wGA Between 10:30am-2:00pm) [Single sample] RIA	Resting (baseline) cortisol levels differ across the four groups (F (3, 101) = 2.72, p = .05). Higher comparing comorbid (anxiety and depression) to controls (2.8 vs. 1.1 units unknown, p=0.01)

Table 1 (continued)

19	(O'Connor et al., 2014)	USA (Clinic)	N=101 (Mean=25y) [#DEP=23 at 20wGA and 13 at 32 wGA]	EPDS + SCID (20 and 32w GA)	Saliva (Mean 21 and 34w GA; Wakening, +45min, +2.5hr, +8hr, +12hr) [Multiple samples] ELISA	Women with a diagnosis of depression had a lower initial waking level (depression x wakeup; r= -0.22, p<0.05). There was no evidence that depression altered the CAR (depression x CAR) or that the overall effect for depression varied across gestation (depression x gestation). The association between depression and cortisol was weaker when depression was evaluated using the EPDS continuous score compared to SCID diagnosis.
20	(O'Keane et al., 2011)	UK (Clinic)	N=65 (19-45y) [#DEP=27]	SCID + HAM-D ≥18 (25, 26 and 36w GA)	Saliva (26 wGA; Morning and evening for 3 consecutive days) [Multiple samples] RIA	Higher mean evening salivary cortisol comparing depressed to controls (7.1nmol/l vs. 4.8nmol/l, p<0.02). Morning salivary cortisol concentrations did not statistically differ (16.6nmol/l vs. 17.2nmol/l, p=0.78)
21	(Pedersen et al., 1993)	USA (Unclear)	N=28 (20-38y) [#DEP=12]	SCID + HRSD (34-38 wGA)	Plasma and 24 hour Urine (38w GA from 8:30-9:00am) [Single urine sample, multiple plasma sample] Assay unclear	No statistically significant comparing morning cortisol of women with a history of major depression to women without a history of major depression (3.4 vs. 3.2 µg/dL logged, p=0.18). 24 hour urinary samples did not statistically differ comparing the two groups (data not shown).
22	(Peer et al., 2013)	Canada (Community)	N=53 (Mean=30y) [#DEP=8 High, 45 Low]	PHQ + EPDS (cutoff 12) (<27w GA)	Saliva (< 27w GA; Waking+30'+60'and between 9-10pm for 2 consecutive days) [Multiple samples] Salimetrics Enzyme Immunoassay	Controlling for wake time, parity, and region of origin, mean evening cortisol levels were significantly higher in women with high levels of depressive symptoms than in women with low levels of depression (6.7nmol/L vs. 2.6nmol/L; p= 0.009). No differences in mean awakening or CAR AUCg were observed.
23	(Pluess et al., 2010)	Germany (Community and Clinic)	N=66 (16-39y) [#DEP=8 in early pregnancy, and 11 in late pregnancy]	EPDS (cutoff 13) (14 and 35-36w GA)	Saliva (14 and 35-36w GA; Waking+30'+45'+60' for 2 consecutive days in early pregnancy, once in the 35-36 wGA) [Multiple samples] LIA	Significant associations between trait anxiety and cortisol levels were observed in early pregnancy, and significant associations between negative life events and cortisol in late pregnancy. No other significant associations between cortisol and psychological measures were observed.
24	(Rouse and Goodman, 2014)	USA (Community and Clinic)	N=77 (18-40y; Mean=30y) [#DEP=49%; 33% in second trimester and 24% in third trimester]	BDI-II (cutoff 14) + SCID (3-4 month of pregnancy; monthly for 3 months)	Urine (<5m pregnant; morning monthly from enrollment to delivery) [Multiple samples] Competitive-binding immunoassay	Second and third trimester cortisol AUC's were not correlated with BDI-II scores at anytime in pregnancy (correlation coefficients ranged from -1.1 to 0.1, p-values > 0.05).
25	(Salacz et al., 2012)	Hungary (Clinic)	N=79 (Mean=37y) [#DEP=15]	BDI-I (cutoff 10) (36-38w GA)	Plasma (36-38w GA; at 8am fasted) [Single sample] RIA	Plasma cortisol did not correlate with BD-I scores (r=-0.06, p=0.5), nor was cortisol a significant predictor of BDI (beta=0.15, standard error=0.11, p-value=0.2)
26	(Shea et al., 2007)	Canada (Clinic)	66 (Mean=31y) [#DEP=14, #DEP+Anxious=19 #Controls=33]	EPDS (cutoff 13) and/or MADRS (cutoff score of 9) (EPDS twice enrollment and mean 28 wGA)	Saliva (25-33 wGA) [Multiple, Waking'+30'+60'] [Multiple samples] EIA	Pearson correlation analyses indicated that the cortisol change was negatively related to current EPDS scores (r= -0.24; p=0.05), but this was not significant when wake-up time and depression medication were controlled for in the linear regression analyses (r=0.28; beta= -0.18; p=0.2). Baseline cortisol concentrations did not statistically differ across the three groups (controls=13.1 nmol/L vs. depressed=12.2 nmol/L vs. depressed/anxious=12.0 nmol/L p="not statistically significant")

Table 1 (continued)

27	(Susman et al., 1999)	USA (Unclear)	59 (Mean=17y) (#DEP=Unclear)	DISC-2.1 (Between 9-21 wGA) [Multiple]	Plasma (Between 9-21 wGA at 8:30am) [Multiple samples] RIA	No significant correlations were found between plasma cortisol concentrations and depression symptoms (results not shown).
28	(Voegtline et al., 2013)	USA (Community and Clinic)	86-107 (Mean=31y) [#DEP=Unclear, only mean depression symptoms provided]	CES-D (Between 24-38 wGA)	Saliva (between 24-38 wGA; Between 1-3pm) [Single sample] EIA	Only for 30-32w GA, an association was observed between cortisol and depression score (adjusted for time of day: r=0.22; p<0.05). Correlations at 33-35 wGA were 0.18, p<10. No correlations were reported for 24-26 wGA, 27-29 wGA, or 36-38 wGA.
29	(Wikenius et al., 2016)	Norway (Community)	181 (Mean=30y) [#DEP=12]	EPDS (cutoff of 11) (Mean=25 wGA)	One-centimeter Hair; Represents past one-month - second trimester [Single sample] RIA	In regression analyses, no association between log-HCC and EPDS sum score adjusted for gestational age, batch, fetal gender, maternal age, maternal education, self-reported maternal health problems and season. HCC did not increase with depression score (r=0.096, p=0.378).

Rows in gray are studies that reported a statistically significant association between maternal cortisol and antepartum depression

wGA gestational age in weeks, *CAR* cortisol awakening response, *DISC* Diagnostic Interview Schedule for Children, *EIA* enzyme immunoassay, *ELISA* enzyme-linked immunosorbent assay, *FPIA* fluorescence polarization immunoassay, *HRSD* 21-item Hamilton Depression Rating Scale, *MADRS* Montgomery Asberg Depression Rating Scale, *EPDS* Edinburgh Postnatal Depression Scale, *PHQ9* 9-item Patient Health Questionnaire, *BDI-I and BDI-II* Beck Depression Inventory versions 1 and 2, *CES-D* Center for Epidemiologic Studies Depression Scale, *SCID* Structured Clinical Interviews, *DISC-2.1* Diagnostic Interview Schedule for Children Version 2.1

the second and third trimesters, and two studies reported no evidence of group by time interactions (Deligiannidis et al. 2016; Hellgren et al. 2013). No clear differences in association were observed across choice of laboratory assay or depression screener.

Study findings according to gestational age of cortisol assessment

Five studies assessed cortisol prior to or at 16-week gestational age (approximately first trimester) (Hoffman et al. 2016; Glynn and Sandman 2014; Goedhart et al. 2010; Luiza et al. 2015; Pluess et al. 2010). Among these studies, one reported a statistically significant association between first-trimester hair cortisol concentrations and antepartum depression scores in week 40 of pregnancy (r = 0.27, p = 0.02) (Hoffman et al. 2016). Eight studies assessed cortisol between 16 to 27-week gestational age (approximately second trimester) (Braithwaite et al. 2016; Davis et al. 2007; Diego et al. 2009; Field et al. 2009; Glynn and Sandman 2014; O'Connor et al. 2014; O'Keane et al. 2011; Hoffman et al. 2016). Among these studies, four reported a statistically significant association. Diego et al. observed elevated mid-morning urinary cortisol concentrations in the second trimester comparing women with and without depression and found that CES-D scores correlated with urinary cortisol concentrations (r = 0.37, p < 0.01) (Diego et al. 2009). O'Connor et al. reported lower initial wakening salivary cortisol in the second trimester among those with depression (r = − 0.22, p < 0.05) but found no evidence of an association between depression and cortisol awakening response (CAR) (O'Connor et al. 2014). Despite no observed difference in second-trimester morning salivary cortisol levels comparing women with and without antepartum depression (16.6 vs. 17.2 nmol/l, p = 0.78), O'Keane et al. observed 67% higher evening salivary cortisol concentrations comparing the two groups (7.1 vs. 4.8 nmol/l, p < 0.02) (O'Keane et al. 2011). Lastly, Hoffman et al. observed an association between second-trimester hair cortisol concentrations and antepartum depression symptom scores at 16 weeks (r = 0.32, p = 0.002) (Hoffman et al. 2016). Sixteen studies assessed cortisol at or after 28-week gestational age (approximately third trimester) (Bjelanovic et al. 2015; Braithwaite et al. 2016; Davis et al. 2007; Deligiannidis et al. 2016; Evans et al. 2008; Field et al. 2009; Glynn and Sandman 2014; Hellgren et al. 2013; Hoffman et al. 2016; Iliadis et al. 2015; Lommatzsch et al. 2006; Monk et al. 2011; O'Connor et al. 2014; Pedersen et al. 1993; Pluess et al. 2010; Salacz et al. 2012). Among these studies, seven reported a statistically significant association, two of which also reported associations in previous trimesters (O'Connor et al. 2014; Hoffman et al. 2016). One study reported elevated third-trimester salivary cortisol among women with antepartum depression at both 8 a.m. (r = 0.239, p = 0.001) and 5 p.m. (r = 0.206, p = 0.005) (Bjelanovic et al. 2015). In another study, first morning urinary cortisol levels were found to be nearly sevenfold higher among the depressed (71.7 vs. 10.5 units, p value = 0.01)

(Field et al. 2009). Nearly twofold increases in 3–7 p.m. serum cortisol levels were observed comparing women with antepartum depression to women without antepartum depression (medians 620 vs. 392 nmol/l; $p < 0.01$) (Lommatzsch et al. 2006). However, correlations between depression scores and cortisol concentrations did not reach statistical significance (data not shown) (Lommatzsch et al. 2006). Two studies reported elevated third-trimester morning salivary cortisol concentrations among small subsets of women with comorbid depression and anxiety, and no difference comparing "depressed only" to healthy controls (Monk et al. 2011; Evans et al. 2008).

Discussion

Reported associations between maternal cortisol and antepartum depression varied across studies. On balance, we observed that (1) the majority of eligible studies reported no statistically significant association between maternal cortisol and antepartum depression ($N = 17$ out of 29), (2) saliva and blood were the most common biological matrices for cortisol detection, (3) morning was the most common time of day for cortisol collection, (4) second and third trimesters were the most common time of pregnancy for cortisol collections, and (5) among studies reporting an association ($N = 12$), second-trimester and third-trimester cortisol assessments more consistently reported an association, and elevated cortisol concentrations were observed in expected recovery periods.

Our review confirms and expands upon previous review articles (Brummelte and Galea 2010; Gelman et al. 2015; Glover and Kammerer 2004; Pariante 2014; Serati et al. 2016; Seth et al. 2016; Workman et al. 2012; Iliadis et al. 2015). For example, a recent review of 47 studies, exceeding our number primarily due to the inclusion of studies assessing depression in the postpartum period as well as during pregnancy (Seth et al. 2016), reported that cortisol awakening responses were blunted in the cases of major maternal depression (including antepartum and postpartum depression). The authors further concluded that hypercortisolemia during pregnancy was associated with transient depressive states, while hypocortisolemia during pregnancy was associated with chronic postpartum depression. Another recent review evaluated a wide range of biomarkers and concluded that hypercortisolemia was associated with depression in the weeks immediately before and after delivery (Serati et al. 2016). Observations of hypercortisolemia among individuals with major depression have been observed in both non-pregnant (Vreeburg et al. 2009) and pregnant populations (Pariante and Lightman 2008; Serati et al. 2016; Seth et al. 2016; Burke et al. 2005). Specifically, individuals (males and females) with major depression have been observed to have higher cortisol concentrations in expected recovery periods where cortisol concentrations are expected to be lower (Burke et al. 2005). Stress-related factors have also been associated with other atypical patterns in cortisol, including blunted and steeper diurnal declines (Stawski et al. 2013; Agbedia et al. 2011). Our review adds to this literature by noting that higher cortisol levels have been observed among pregnant women with antepartum depression using matrices reflecting evening levels and that this may be particularly noticeable in the second and third trimesters when circulating cortisol levels are at their highest.

Study design methodologies varied widely, impacting comparisons across eligible studies. First, few of the eligible studies reported on the association between maternal cortisol and antepartum depression in the first trimester of pregnancy. Therefore, we cannot distinguish whether the association between maternal cortisol and antepartum depression is more common in the second and third trimesters due to physiologic changes later on in pregnancy, or whether it appears more common due to limited data in the first trimester of pregnancy. Second, some studies may have been underpowered to detect an association due to small sample sizes. Third, studies likely differed in their determination of gestational age (example: self-reported last menstrual period vs. ultrasound). Therefore, comparison across studies within our trimester categories should be interpreted with some caution. Fourth, the majority of studies utilized biological matrices that reflected acute cortisol levels in the 1 to 24 hours prior to collection (saliva, blood, and urine). Such matrices allow investigators to observe deviations in expected diurnal patterns, however are limited in their ability to assess differences in long-term cortisol secretion. Two studies utilized hair that reflected long-term cortisol levels in the months prior to collection. A commonly cited limitation of this biologic matrix is the potential for cortisol degradation and leaching (Russell et al. 2012). Despite the aforementioned caveats, an understanding of both acute and long-term maternal cortisol levels is necessary in order to further our understanding of the underlying neurobiological pathways at play in antepartum depression.

Our findings highlight specific gaps in the literature for the association between maternal cortisol and antepartum depression. These gaps include the need for findings that integrate multiple maternal cortisol collections spanning all trimesters of pregnancy. Maternal cortisol collections ranging from the first trimester to delivery would allow for analyses of cortisol trajectories across the pregnancy period. Such analyses would help to determine whether women with antepartum depression present with different long-term cortisol trajectories. An additional gap noted in our review of the literature is the need for data from low-income and middle-income countries, where the burden of antepartum depression is often two to three times higher

(Lara et al. 2009; Schatz et al. 2012; Barrios et al. 2015; Shidhaye and Giri 2014). Therefore, additional research across a diverse range of study populations and study participants is warranted.

Conclusion

Antepartum depression is an important research priority, and reviews of the existing literature help shed light on strategic next steps, thereby accelerating the pace at which research findings are translated into clinical practice. These strategic next steps potentially include the evaluation of maternal cortisol secretion profiles across pregnancy using longitudinal study design approaches and an expansion of the research question to diverse study populations and participants.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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