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A systematic review of cortisol, thyroid stimulating hormone and prolactin in peripartum women with major depression

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Introduction

Major depression (MD) is amongst the most predominant mental health disorders in the United States. Women are twice as likely as men to experience MD during their lifetimes, and lifetime prevalence of MD in women is 6–17% (Kessler 2003). In one study, almost two-thirds of pregnant women met Diagnostic and Statistical Manual (DSM)-IV criteria for a major depressive episode (MDE) within the past year when interviewed by a clinician, yet these women were unaware of their diagnosis and had not received mental health treatment (Ko et al. 2012). Marcus similarly reported that only 20% of women who met criteria for MD during pregnancy were engaging in treatment (Marcus 2009). Depression in the 12 months postpartum occurs at a rate of 9–22% (Vesga-Lopez et al. 2008; Gavin et al. 2005; Wisner et al. 2013). If untreated, peripartum MD is associated with detrimental outcomes (Brockington et al. 2017); for mothers, these include increased risk of smoking, substance abuse, poor nutrition, marital conflict, and subsequent recurrence of depression (Le Strat et al. 2011; Stewart and Vigod 2016). For offspring, detrimental outcomes include preterm birth, poor fetal growth, low birth weight, dysregulated attention and arousal (which can progress to attention deficit hyperactivity disorder), impaired adaptive functioning and anxiety, decreased cognitive ability, and elevated stress reactivity in the teenage years (Muzik et al. 2009; Grote et al. 2010; Bernard-Bonnin 2009; Ciesielski et al. 2015; Halligan et al. 2007; Barry et al. 2015). Treatment of maternal depression leads to a decrease in child psychopathology (Weissman et al. 2006). Clearly, the prevalence of peripartum MD, its low rates of recognition and treatment, and its lasting deleterious consequences for mothers and children make understanding the pathophysiology and treatment of this condition a high public health priority.

Aim of Current Review

In addition to the susceptibility of mood changes, the peripartum period is characterized by rapid and significant changes in hormones, including cortisol, thyroid stimulating hormone (TSH), prolactin, gonadotropins and gonadal steroids (Bloch et al. 2003; Parry et al. 2003; Parry et al. 2006). To understand this temporal association and a potential causal link

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between depression and changes in non-gonadal hormones during the peripartum period, we systematically reviewed published findings of cortisol, TSH and prolactin in women with MD. Our goal was to determine if any of these three hormones had confirmed correlations – positive or negative – in women with peripartum MD.

Methods

Search

Because structured clinical interviews have greater sensitivity to accurate diagnosis compared with self-reported measures (Parcells 2010), we focused on MD diagnosed by clinical interview, most commonly by the Structured Clinical Inventory for DSM Disorders-IV (SCID-IV). Studies using self-report screening measures as the sole clinical instrument were not included in this review, nor were studies focused on postpartum “blues” or subsyndromal depressive symptoms. Articles were identified via PubMed or Web of Science using specific search criteria, e.g. “depression,” “pregnancy”, “postpartum”, and “cortisol” for the first section. Additional citations were identified as “Similar Articles” in PubMed. This procedure is further explained as a flow chart in Fig. 1.

Inclusion and Exclusion Criteria

Articles had to meet the following criteria to be included in this review: (1) publication date between 1996 and August 1, 2016; (2) written in English; (3) studies in humans; and (4) diagnosis of MD made by a clinician. In addition, multiple measurements of cortisol were required to account for diurnal variation, or conversely, urine collection over time; for TSH and prolactin, one plasma sample was required. Articles were excluded if they were case reports or review articles.

Data Extraction and Quality of Studies

Data extracted from each study included: author, year, timing of sample, source of sample and method of sample measurement (cortisol only), method of MD diagnosis, use of other depression scales, and a brief description of reported outcomes. The quality of each study was determined using the Newcastle-Ottawa Quality Assessment Scale. A Newcastle-Ottawa Score (NOS) of 9 indicates the highest quality and therefore lowest risk of bias, whereas score of 3 or lower confers a high risk of bias; a score of 4–6 indicates a moderate risk of bias (Deeks et al. 2003). Additionally, limitation(s) are reported in the second to last column. In the studies where no limitations were found in terms of inclusion in this review, “N/a” is listed in the limitations column, meaning “not applicable.”

Cortisol in Antepartum and Postpartum Major Depression

Cortisol, the steroid hormone upregulated by hypothalamic-pituitary-adrenal (HPA) axis signaling in the setting of stress, is elevated in depressed patients (Carroll et al. 1976; Linkowski et al. 1985). Cortisol secretion follows a circadian rhythm, rising in early morning to a mid-morning peak, then declining in the evening before sleep onset. Altered sleep onset, offset, and duration change cortisol production (Balbo et al. 2010). As shown in Fig. 1, 15 studies were identified that included women in the peripartum period who were

diagnosed with MD by a clinician and had repeated cortisol measures to account for circadian rhythm variation (Table 1). These studies varied in cohort characteristics, timing, frequency and source (saliva, serum, urine) of cortisol sampling. They have been grouped by pregnancy status – i.e., pregnant versus postpartum – followed by interventional studies.

Field et al. (2006, 2008) published studies on a cohort of 430 pregnant women recruited from a university hospital. During the 2nd trimester (approx. 20 weeks gestation), 172 (40%) of these women were determined to have either MD or dysthymia by structured clinical interview. Morning urinary cortisol was collected at this time point and again during the 3rd trimester (approx. 32 weeks gestation), during scheduled fetal ultrasound appointments. Spot urinary cortisol was *higher* in depressed women compared to pregnant healthy control subject (HCS) during the 2nd trimester. Additionally, 2nd trimester depression was predictive of 3rd trimester depression, anxiety, and sleep disturbance. During 3rd trimester sampling, however, cortisol was not higher in depressed women. Interestingly, depressed women had shorter gestations by approximately 1.5 weeks compared to HCS, and the newborns from depressed women had lower birth weights. In a larger study by these investigators (Field et al. 2010), 911 subjects were recruited from university hospital prenatal clinics and subsequently followed from the 2nd trimester of pregnancy onwards; 181 (19.9%) were diagnosed with MD, 77 with anxiety, and 308 (33.8%) with comorbid MD and anxiety. Morning urinary cortisol was collected at approx. 20 and 32 weeks gestation, and 2 days postpartum. Contrary to their prior study (Field et al. 2006), no difference in cortisol was detected between women with vs. without a diagnosis of MD or anxiety. The high rate of depression in this larger study (54%) and their earlier one suggest that low diagnostic specificity may have contributed to the failure to reproduce findings across studies (Field et al. 2010).

Among 182 women in their 2nd trimester of pregnancy, Evans et al. (2008) identified 16 (8.8%) with MD, 34 with anxiety, and 9 (4.9%) with comorbid MD and anxiety. At 36 weeks gestation, salivary cortisol was collected at three time points as the subjects completed computer-based tasks: between 1030–1130, then 30 and 90 minutes later. The computer-based tasks included a Stroop color-word matching task, a mental arithmetic task, or a controlled breathing task. Women with comorbid MD and anxiety had higher cortisol levels at multiple time points. However, cortisol levels did not differ between women diagnosed with MD or anxiety alone vs. pregnant HCS.

Parcells (2010) studied depression, anxiety, and stress in 59 pregnant women, but only 28 research participants completed both time points. Salivary cortisol levels were sampled at 26–28 and 32–34 weeks gestation, between 1000–1130. Rates of MD by clinical interview were 32.1% and 23.1% during the 2nd and 3rd trimester, respectively. No association between cortisol and MD was identified. The reduced rate of depression in the 3rd vs. 2nd trimester suggests differences in these cohort characteristics, which may reflect attrition of the most severely depressed women, or it may represent over-identification of depressed subjects since the rate of 32.1% is higher than the general population.

Rouse and Goodman (2014) compared urinary cortisol (from waking until noon) of pregnant women diagnosed with MD (n=23) vs. pregnant HCS (n=54); samples were collected

monthly throughout pregnancy. Cortisol levels increased over the course of pregnancy, but the levels did not differ across groups.

O'Connor et al. (2014) recruited over 100 pregnant women in their first trimester; 23 were diagnosed with MD. Salivary cortisol was measured 5 times daily – at awakening, and 45 minutes, 2.5 hours, 8 hours, and 12 hours later – during the 2nd (approx. 21 weeks) and 3rd trimesters (approx. 34 weeks). Compared to pregnant HCS, women with MD had significantly *reduced* levels of morning cortisol, follows by higher cortisol levels later in the day.

The first study focused on the postpartum period, Harris et al. (1996) examined salivary cortisol twice a day (0800 and 2200) from 120 women, from 2 weeks antepartum until 35 days postpartum. Seven of these women developed MD by 6 weeks postpartum. Compared with non-depressed women, the depressed women had lower evening cortisol levels in the immediate postpartum period, but did not differ in morning cortisol levels.

In a pilot study, Parry et al. (2003) investigated plasma cortisol in both pregnant women (3 with MD, 2 HCS) and postpartum women (13 with MD, 2 HCS), via frequent sampling – every 30 minutes from 1800 until the following morning at 1100. Repeated, frequent cortisol measures allow for cosine analysis to determine: 1) amplitude, or half the value of a cosine function; 2) mesor, or midpoint of a cosine function; and 3) acrophase, or peak value of a cosine function. During pregnancy, cortisol amplitude was *lower* in depressed vs. non-depressed women. Postpartum, cortisol amplitude was *higher* in depressed vs. non-depressed women. Both ante- and postpartum, the cortisol acrophase was *earlier* in depressed vs. non-depressed women. The use of repeated, frequent sampling in this study identified: 1) the importance of time of day for cortisol measurement, and 2) that absolute cortisol levels change during pregnancy and postpartum.

Taylor et al. (2009) identified 21 women with MD approximately 8 weeks postpartum, 30 postpartum women without depression and 21 non-perinatal HCS. Salivary cortisol samples were collected at awakening, and 30 minutes, 3 hours, and 12 hours later. Compared with HCS, non-depressed, postpartum women showed a similar cortisol secretion pattern, with a rise between the first and second salivary collections, followed by a decline throughout the rest of the day. Cortisol from depressed, postpartum women, however, was stable between the first and second salivary collections, followed by a decline similar to the other subjects. The authors commented that this lack of rise in morning cortisol had been similarly demonstrated in women with posttraumatic stress disorder (Wessa et al. 2006).

In women who were 6 months postpartum, de Rezende et al. (2016) obtained salivary cortisol at awakening, and 30 minutes, 3 hours, and 12 hours later. The study included: 37 depressed, postpartum women; 42 euthymic, postpartum women; and 25 non-perinatal HCS. Both groups of postpartum women demonstrated attenuation of morning cortisol awakening response (CAR) compared to HCS, but it was more pronounced in the depressed, postpartum women. Additionally, this cohort manifested significantly *lower* cortisol at awakening, 30 minutes later, and 3 hours later compared to non-postpartum HCS. The EPDS scores of the depressed, postpartum subjects were negatively correlated with the CAR.

Four interventional studies met our review criteria. Okun et al. (2011) studied 56 pregnant, euthymic women at "high risk" (HR) for MD based on a past history of MD, including postpartum depression (PPD), were randomized to receive nortriptyline, sertraline, or placebo. Serum cortisol samples and self-reported sleep quality were collected biweekly during the first 17 weeks postpartum. Cortisol initially declined but then returned to gestational levels by 11–17 weeks postpartum. Twelve (21.4%) HR women had a recurrence of MD during this period, which was predicted by subjective measure of poor sleep quality but not by cortisol levels.

In a study by Urizar and Muñoz (2011), pregnant women identified as HR based on a past MDE and current depressive symptoms were randomized to two groups: cognitive-behavioral therapy (CBT) for stress management (n=24) vs. usual care (n=33) during their 2nd trimester. Salivary cortisol levels were obtained 45 minutes after awakening and at 2000 at three time points: during pregnancy, and 6 months and 18 months postpartum. Samples were compared to pregnant HCS (n=29). No differences in cortisol were detected during pregnancy and 6 months postpartum among the three cohorts. At 18 months postpartum, *lower* cortisol levels were detected in the group of mothers at HR for depression who attended more CBT classes, by interindividual comparison.

In another CBT-interventional study, Richter et al. (2012) used the Munich-Composite International Diagnostic Interview (CIDI) to identify subclinical depression in women during their first trimester, who then were randomized to receive CBT (n=21) vs. no intervention (n=40). Salivary cortisol was obtained 5 times during the course of a day – awakening, 30 minutes later, 1100, 1700, and 2200 – at three different dates: 2nd trimester baseline (approx. 23 weeks gestation), 3rd trimester post intervention (approx. 34 weeks gestation), and 3 months postpartum. In the CBT group, morning cortisol (30 minutes after awakening) was *reduced* vs. no intervention after 4–8 sessions of CBT in the antenatal period and 3 months postpartum.

In a fourth interventional study, Field et al. (2013) randomized pregnant women diagnosed with MD to 12 weekly sessions of yoga (n=40) vs. support group (n=39). Salivary cortisol samples and depression self-rating were obtained mid-morning, before and after the first and last session of yoga or support group (exact time not reported). Both treatments reduced depression, anxiety, and anger. Salivary cortisol was increased later in pregnancy, as expected, but was significantly *reduced* in samples collected immediately after vs. before the intervention.

In summary, the relationship of peripartum MD and cortisol has been studied using a range of different methodologies, with different diagnostic instruments, source, timing, and frequency of cortisol sampling, as well as with interventions. The absolute level of cortisol rises over the course of pregnancy (Bloch et al. 2003; Parry et al. 2003; Field et al. 2010; Rouse and Goodman 2014). Convergent studies reported *reduced* serum or salivary CAR in pregnant women with MD, which normalized later in the day (O'Connor et al. 2014; Parry et al. 2003); such findings were not detected with urinary cortisol (Field et al. 2010; Rouse and Goodman 2014). Evans et al. (2008) determined that salivary cortisol was elevated in women with comorbid MD and anxiety but not in MD alone, which was consistent with

subsequent studies by Parcells (2010; salivary) and Field et al. (2008; urinary). Only one study, which included diagnoses of MD as well as dysthymia in their subjects, determined that urinary cortisol was elevated in depressed women vs. HCS in the 2nd but not the 3rd trimester (Field et al. 2006). Findings among three interventional studies during pregnancy (Field et al. 2013; Richter et al. 2012; Urizar and Muñoz 2011) suggest that CBT, stress management or yoga may all reduce cortisol levels in peripartum MD, though methodological differences preclude direct comparison across studies. The one interventional study comparing medications – two different antidepressants – to placebo in pregnant women at HR for MD did not show a connection between cortisol levels and a diagnosis of MD (Okun et al. 2011).

In postpartum, depressed women, divergent findings were reported. Parry et al. (2003) reported *elevated* serum cortisol in a small pilot study, which included different time points during the postpartum period. In contrast, Harris et al. (1996) reported *lower* evening salivary cortisol at one month postpartum. Taylor et al. (2009) reported no rise in morning salivary cortisol in depressed women at two months postpartum. Similarly, de Rezende et al. (2016) observed an attenuated CAR at 6 months postpartum in both depressed and healthy controls compared to non-peripartum HCS, but it was more pronounced in the depressed women.

As described in Table 1, the studies during pregnancy with the lowest risk of bias as determined by NOS found either no correlation between MD and cortisol (Okun et al. 2011; Rouse and Goodman 2014) or a reduced CAR in women with MD (O'Connor et al. 2014). Both of the postpartum studies with the lowest risk of bias according to the NOS reported an attenuated CAR in women with MD (Taylor et al. 2009; de Rezende et al. 2016). Thus, the studies reviewed here suggest a complex pattern, in which cortisol rises across pregnancy, and compared to euthymic women, it is *reduced* in morning samples from patients with both antepartum MD or PPD diagnosed at 2-to-6 months postpartum.

TSH in Antepartum and Postpartum Major Depression

TSH, a neuroendocrine hormone influenced by sleep and circadian rhythmicity and exercise, is characterized by low daytime levels followed by a rapid increase and peak near the time of sleep onset (Leproult et al. 1997). TSH increases with sleep deprivation (Sack et al. 1988), and is modulated by light exposure (Kripke et al. 2010). During exercise, TSH rises and remains elevated, and this effect is more pronounced with evening exercise (Scheen et al. 1998). Leproult et al. (2001) determined that TSH is further impacted by postural changes, sleep-wake transition, and social stimulation, all of which fluctuate in the peripartum period due to changes in body habitus and infant care. TSH – and subsequently 3,5,3-triiodothyronine (T3) and thyroxine (T4) – rise during the physiologic hypervolemic state of pregnancy to optimize fetal development (Soldin et al. 2004). Postpartum, some women experience thyroiditis due to production of thyroid antibodies (Lazarus et al. 1996), manifesting a transient hyperthyroidism followed by transient hypothyroidism within the first 6 months postpartum; these thyroid changes, however, are only sometimes accompanied by depressive symptomatology (Lazarus et al. 2002). In clinically normal individuals, TSH declines to pre-pregnancy levels in the early postpartum period (Soldin et al. 2004). The

focus of this review is confined to changes in TSH (and not T3, T4 or thyroid antibodies) in relationship to peripartum MD (Table 2), which included 7 studies.

Abou-Saleh et al. (1996) obtained blood samples from 34 women at 7 days postpartum, between 0900 and 1000. By 8 weeks postpartum, 4 women had developed MD based on the Present State Examination (PSE). No difference in TSH was detected in the 4 depressed vs. 30 non-depressed women.

In a study by Kent et al. (1999), among 748 Austrailian women at 6 months postpartum, 44 (5.9%) had elevated TSH, whereas 25 (3.3%) had reduced TSH, compared to 670 women with normal TSH. By CIDI interview (DSM-III-R criteria), 76 (9.4%) women had MD; no association was detected between TSH levels and MD.

Kuijpens et al. (2001) recruited 310 women from routine prenatal checks. At 12 and 32 weeks gestation and at 4, 12, 20, 28, and 36 weeks postpartum, blood samples were collected at home visits. Research Diagnostic Criteria (RDC) diagnosed major and minor depression in 158 women (54.3%) throughout the course of the study; 117 women (40.1%) were diagnosed postpartum. No association between thyroid dysfunction and MD was identified.

From a community hospital, 641 women were recruited by Lucas et al. (2001), between 36 weeks gestation and 4 days postpartum. Blood samples for TSH were gathered at 1, 6, 9, and 12 months postpartum. MD was diagnosed by DSM-III-R criteria in 11 women, none of whom had abnormal TSH levels; in contrast, 56 (11%) of the non-depressed women had abnormal (elevated or reduced) TSH levels.

Oretti et al. (2003) studied 115 thyroid antibody-positive, pregnant women vs. 123 antibody-negative, pregnant women recruited at approximately 16 weeks of pregnancy. The women were assessed for MD by RDC at 8, 12, 20, and 28 weeks postpartum, with concurrent blood sampling for TSH. No association was detected between thyroid dysfunction – either positive thyroid antibody status or altered TSH – and MD.

Plaza et al. (2010) diagnosed 104 women with MD within the first 6 months postpartum. Of these, 6 women (6%) had hyperthyroidism (low TSH), and one women (1%) had hypothyroidism (elevated TSH). The authors concluded that there was no relationship between alterations in TSH and MD.

Parry et al. (2003) examined plasma TSH in both pregnant women (3 with MD, 2 HCS) and postpartum women (13 with MD, 2 HCS), in the protocol described above for cortisol measurements. During pregnancy, TSH acrophase occurred *later* in depressed vs. non-depressed women; postpartum, TSH acrophase occurred *earlier* in depressed vs. non-depressed women. TSH amplitude was *lower* in depressed vs. non-depressed women both during pregnancy and postpartum.

The studies included in this review were designed to determine if TSH is associated with MD in the peripartum period. The one study that identified TSH reductions and shifted acrophase (Parry et al. 2003) utilized frequent, repeated sampling in a pilot study. In the two

studies deemed to have a low risk of bias by the NOS, there was no association between thyroid dysfunction and peripartum MD (Kent et al. 1999; Oretti et al. 2003). Conceivably, abnormal signaling of the hypothalamic-pituitary-thyroid axis or thyroid antibodies in peripartum MD might occur in other thyroid hormones and/or thyroid antibodies that were not the focus of this review. Nonetheless, current evidence is insufficient to link abnormal TSH levels with peripartum MD.

Prolactin in Antepartum and Postpartum Major Depression

Prolactin initiates and maintains lactation, and while it is not circadian-dependent (like cortisol and TSH), it is dependent on sleep (Linkowski et al. 1998). Prolactin increases 20–50 times in healthy pregnancy compared with nulliparity (Moult and Besser 1981), and in non-lactating women, levels normalize within three weeks of parturition (Hendrick et al. 1998). Estrogen stimulates prolactin secretion (Marshall et al. 1988), and similar to prolactin, estrogen rapidly declines after parturition (Liu et al. 1983). In breastfeeding women, the level of prolactin remains elevated after birth, and declines gradually over the course of several months (Liu et al. 1983). Given these sizable peripartum changes, prolactin has been investigated for its possible role in mood changes, particularly in relation to breastfeeding (Alder and Cox 1983; Kuevi et al. 1983; Harris et al. 1989; O'Hara et al. 1991). We found three studies that included research subjects with a clinical diagnosis of MD (Table 3).

Using the protocol described above for TSH measurements, Abou-Saleh et al. (1998) also measured plasma prolactin in 34 postpartum women between 0900 and 1000, 7 days after parturition. Eight weeks postpartum, 4 of 34 women were diagnosed with MD. Day 7 prolactin was significantly *lower* in women with MD vs. women who did not develop MD. Postpartum women who had previously experienced MD had *reduced* prolactin and were less likely to breastfeed. Previous literature supports the finding that depressed women tend not to breastfeed (Ystrom 2012; Dennis and McQueen 2009; Henderson et al. 2003); 22 out of 34 women in this study were breastfeeding (breastfeeding status of the 4 depressed women was not reported). In addition to the potential confound of breastfeeding, it is possible that prolactin determination 7 days after parturition is not representative of longitudinal alterations in the postpartum period.

Parry et al. (2003) investigated serum prolactin in both pregnant women (3 with MD, 2 HCS) and postpartum women (13 with MD, 2 HCS), in the protocol described above for cortisol measurements. Prolactin was *higher* in depressed vs. non-depressed subjects, both in the antepartum and postpartum periods. Among the depressed women, prolactin was *higher* in breastfeeding vs. non-breastfeeding women.

Okun et al. (2011) studied 56 pregnant, euthymic women at HR for MD were randomized to receive nortriptyline, sertraline, or placebo. Serum prolactin and self-reported sleep quality were collected biweekly in the postpartum period through 17 weeks. Prolactin levels declined in the postpartum period and stabilized at about 4 weeks postpartum. They found no association between prolactin and MD when diagnosed postpartum by DSM-IV criteria in 21.4% of the cohort.

In summary, studies focusing specifically on the association between peripartum MD and prolactin levels report discrepant findings using different study protocols. Prolactin was reduced 7 days postpartum in women who later developed MD (Abou-Saleh et al. 1998); it was also reported to be elevated in pregnant and postpartum depressed women when measured via frequent sampling overnight (Parry et al. 2003). A third study, with the least bias as determined by the NOS, reported no difference in prolactin in depressed vs. non-depressed women based on longitudinal sampling over 17 weeks postpartum (Okun et al. 2011). Sampling differences, breastfeeding status and its associated sleep dysregulation may have contributed to discrepant findings across these reports.

Discussion

The peripartum period is characterized by a significant increase in risk for a MDE and by substantial changes in levels of hormones. This curious overlap of mood disturbances and endocrine shifts raises a critical question: are these two processes linked? To examine the extant evidence, we reviewed published literature reporting MD in the antepartum and postpartum periods in relation to cortisol, TSH, and prolactin. In healthy women, all three hormones have been shown to rise during the course of pregnancy and then fall during the postpartum period, although at different rates (Bloch et al. 2003; Parry et al. 2003). A specific hormone would be considered to be associated with peripartum MD if the level or circadian pattern of that hormone differed significantly in healthy vs. depressed peripartum women, or in women who subsequently did vs. did not develop a MDE. This review identified that timing and frequency of sampling was critically important in identifying changes in the levels of circadian- and/or sleep-dependent hormones, especially during pregnancy and postpartum. Other variables that may impact the ability to detect postpartum hormonal shifts include the source of the hormonal sample and the effects of breastfeeding.

Of these three hormones – cortisol, TSH, and prolactin – evidence was most suggestive of a link between MD and abnormal cortisol activity, although the nature of this association is complicated by the timing and source (serum, saliva, or urine) of sample collection. In pregnant women, the most consistent finding was an association between MD and reduced cortisol in the morning, but not at other times; this was determined by both serum and salivary samples (O‘Connor et al. 2014; Parry et al. 2003). After delivery, the most consistent finding – based on salivary cortisol levels – was an association of MD with reduced morning cortisol (Taylor et al. 2009; de Rezende et al. 2016). Seth et al. (2016) also recently concluded that maternal MD was associated with cortisol dysregulation, more specifically, by reduced morning cortisol. Among other conclusions, this review underscored the importance of repeated cortisol sampling and structured diagnostic procedures to ensure study reliability (Seth et al. 2016), which is congruent with the findings reported here.

The observation that morning cortisol is comparatively reduced in peripartum MD may seem paradoxical, but it is possible that women with peripartum MD have a differing conveyance of cortisol signaling compared to euthymic women. While the women with MD may not experience the normal full daily range of cortisol (i.e., peak of cortisol amplitude) experienced by their healthy counterparts, it is plausible that their cortisol receptors produce an altered signal that no longer requires this brief pulsatile increase of morning cortisol. In

fact, Buss and colleagues found attenuation of the CAR in healthy pregnancies as the duration of gestation progressed (Buss et al. 2009), and de Rezende and colleagues made the same observation in healthy, postpartum women compared to non-peripartum women (de Rezende et al. 2016). A complete understanding of this mechanism, however, remains to be understood.

In contrast to cortisol, evidence linking abnormal levels of TSH or prolactin to peripartum MD is less compelling. It should be noted that studies reporting hypothalamic-pituitary-thyroid signaling other than via TSH were not included in this review. One study using frequent, repeated sampling reported an association of MD with reduced TSH levels both during and after pregnancy, with delayed acrophase during pregnancy and advanced acrophase postpartum (Parry et al. 2003). With regards to prolactin, only three studies were identified that assessed prolactin levels in MD in the peripartum period, and these studies yielded differing results, potentially reflecting variability introduced by differences in both sleep and breastfeeding across these studies.

This review has several limitations, including the exclusion of many articles pertaining to peripartum women with depressive symptoms and measurements of cortisol, TSH or prolactin. However, we required a clinical diagnosis of MD to ensure objective findings, rather than subjective report. We included comparisons of the risk of bias amongst the studies using the Newcastle-Ottawa Quality Assessment Scale; while this scoring system is a widely-used aid in the determination of study quality in systemic reviews, we acknowledge that it is an imperfect tool (Seehra et al. 2016). Nonetheless, it was helpful in comparing and prioritizing quality of studies.

Brockington and colleagues recently emphasized the need for more research into the causation, treatment and prevention of mental illness during the peripartum period to prevent disruption of the mother-infant relationship and other potential negative outcomes for both mother and child (Brockington et al. 2017). The focus of the present review was limited to cortisol, TSH, and prolactin, but many hormonal changes occur over the course of pregnancy and postpartum, and these other hormonal changes may be associated with increased (or decreased) risk for peripartum MD (Bloch et al. 2003). For example, Moura et al. (2016) recently reviewed reports suggesting that reduced peripheral oxytocin levels in the antepartum and postpartum periods were associated with an increased risk of depressive symptoms. Although our current understanding of these many hormones in the peripartum period has not identified a predictive biomarker for MD, it is clear that maternal depression has a deleterious impact not only on the mother, but also on the infant – via disturbances in the development of motor, socio-emotional and cognitive abilities (Karam et al. 2016). Identifying such predictive biomarkers and the underlying hormonal mechanisms that contribute to a risk for depression in women during this critical time period should thus be a high public health priority.

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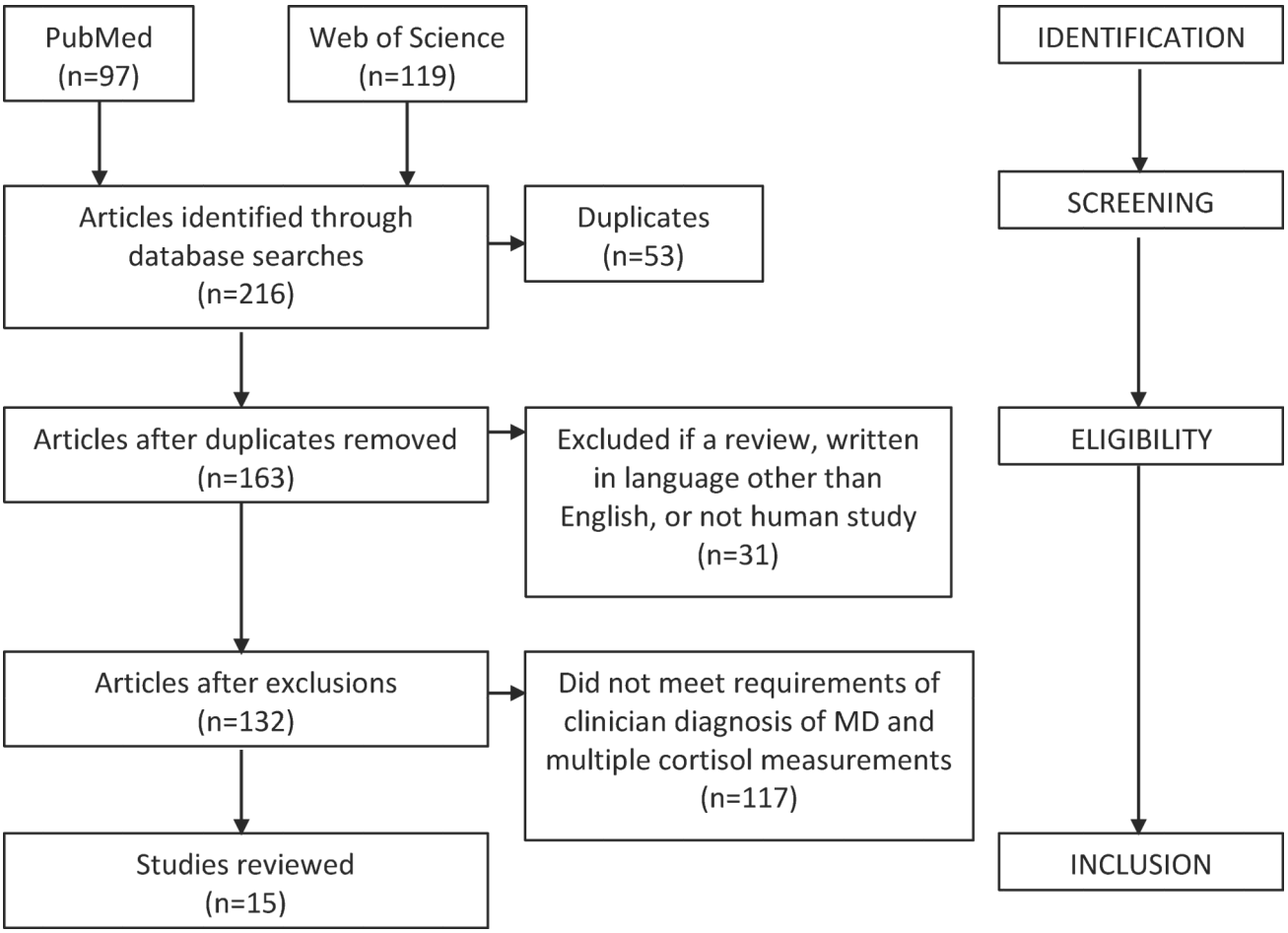

Figure 1.
Flow chart demonstrating search procedure for cortisol
MD major depression

Table 1

Cortisol in Peripartum Major Depression

Authors	Subjects	Source & Measurement	Methods	Depression scale(s)	Reported Outcomes	Limitation(s)	Newcastle-Ottawa Score (NOS) *
Harris et al. (1996)	N=127 (N=120 healthy pregnant women, N=7 depressed pregnant women)	Saliva; RIA	Twice a day (0800 and 2200) from 2 weeks prior to delivery until 35 days PP	SCID	Lower levels of evening cortisol in the immediate postpartum period associated with postnatal depression	Collection times may have missed peak cortisol level; low rate of MDD (7%); relatively short duration of follow up (6 weeks)	5
Parry et al. (2003)	N=20 (N=2 healthy pregnant women, N=3 depressed pregnant women, N=2 healthy postpartu m women, N=13 depressed postpartu m women)	Serum; unspecifie d	Overnight every 30 min from 1800 until 1100	SCID (HDRS, BDI)	Increased cortisol in PP depressed women compared to controls, and decreased cortisol in pregnant depressed -but insufficient data to obtain effect size	Small sample size	5
Field et al. (2006)	N=430 (N=258 healthy pregnant women, N=172 depressed pregnant women)	Urine; RIA	20 and 32 weeks gestation, and at 2 days PP	SCID (for depression or dysthymia)	2nd trimester depression correlated with increased cortisol, also predictive of 3rd trimester depression & anxiety, sleep disturbance; 3rd trimester depression not correlated with change in cortisol	40% rate of depression (likely elevated due to inclusion of dysthymia diagnosis); variability of time of spot urine collection	4
Field et al. (2008)	N=430 (N=344 healthy pregnant women, N=86 depressed pregnant women)	Urine; RIA	20 and 32 weeks gestation, and at 2 days PP	SCID (for depression or dysthymia)	Cortisol elevated in depression during the 2nd but not 3rd trimester; correlated shorter gestational age with lower birth weight	20% rate of MDD or dysthymia, different from previous report in 2006; variability of time of spot urine collection	5
Evans et al. (2008)	N=182 (N=123 healthy pregnant women, N=16 depressed pregnant women, N=34 anxious pregnant women, N=9 comorbid pregnant women)	Saliva; RIA	Thrice in one day -baseline, in anticipatio n of task, and post-task -obtained at 36 weeks gestation	SCID (CES-D, PES)	Comorbid depression and anxiety correlated with higher cortisol at all 3 time points, but depressed and anxious cohorts no different from control	Time gap between diagnosis and accrual of sample; >25% samples excluded from analysis due to insufficient saliva	5
Taylor et al. (2009)	N=72 (N=30 healthy postpartu m women, N=21 depressed	Saliva; EIA	Awakenin g, 1/2 hour, 3 hours, and 12 hours later -obtained for 2	SCID (EPDS >13 to stratify results)	No rise in cortisol 30 min after awakening in depressed women, as was demonstrate d in other 2 cohorts	40% rate of depression	8

Authors	Subjects	Source & Measurement	Methods	Depression scale(s)	Reported Outcomes	Limitation(s)	Newcastle-Ottawa Score (NOS)*
	postpartu m women, N=21 non-perinatal women)		days in a row at 6–8 weeks postpartu m				
Field et al. (2010)	N=911 (N=345 healthy pregnant women, N=181 depressed pregnant women, N=77 anxious pregnant women, N=308 comorbid (depresse d and anxious) pregnant women)	Urine; RIA	20 and 32 weeks gestation, and at 2 days PP	SCID (STAI, CES-D, STAXI, BIS)	No differences in cortisol	54% rate of depression; inconsistent with previous study by same authors	6
Parcells (2010)	N=59 (all pregnant women)	Saliva; STAT Fax 2100 microplat e reader	26–28 weeks gestation (1000–1130) and at 32–34 weeks (1000–1130)	SCID (BDI)	No significant association of MD with cortisol	Homogenou s sample population (91.4% African-American; 77.2% unpartnered); sole cortisol measure at 2 time points; only 28 women completed both visits	4
Okun et al. (2011)	N=56 (all pregnant women with Hx of MDD; randomize d to N=20 nortriptylin e, N=10 sertraline, N=26 placebo)	Serum; RIA	Postpartu m at 2, 3, 4, 6, 8, 11, 14, and 17 weeks	clinician interview (HDRS)	Cortisol did not correlate with depressive symptoms; cortisol initially decreased and then increased back to gestational values between 11 & 17 weeks PP; poor sleep quality over 17 weeks PP was predictive of recurrent MDD (measured via self report)	High risk population recruited during pregnancy, with 20% who developed PPD; lack of repeated measures in same day	7
Urizar and Muñoz (2011)	N=86 (57 pregnant women at high risk for MDD with N=24 randomize d to CBSM vs. N=33 to UC; N=29 healthy pregnant women)	Saliva; ELISA	Twice a day (45 min after awakenin g and 2000) during 2nd trimester of pregnancy , at 6 months PP, and at 18 mo PP	“screening ” interview using Maternal Mood Screener (CES-D)	At 6 months PP, no difference in cortisol but higher perceived stress in CBSM moms who attended more classes; at 18 months PP, lower cortisol in women who attended more CBSM classes	High risk for MDD but did not have Dx at initiation of study; only 2 cortisol samples over the course of the day	6
Richter et al. (2012)	N=61 (pregnant women with subclinical depression randomize d N=21 to CBT	Saliva; ELISA	Cortisol x5 for CAR at pre-interventio n (2nd trimester), antepartu m (3rd	M-CIDI for subclinical depressive pathology	Intervention subjects showed decreased CAR after 4–8 CBT sessions (focused on stress, anxiety, depression)	Focus on subclinical depression, not MDD	6

Authors	Subjects	Source & Measurement	Methods	Depression scale(s)	Reported Outcomes	Limitation(s)	Newcastle-Ottawa Score (NOS)*
	interventio n vs. N=40 to UC)		trimester), and at 3 months PP				
Field et al. (2013)	N=79 (depresse d pregnant women randomize d to N=40 yoga group and N=39 social support group)	Saliva; unspecifie d	Before and after 1st & last sessions	SCID (EPDS, CES-D, POMS)	Both intervention s resulted in decreased depression, anxiety, anger, and improved relationship s; decreased cortisol after sessions compared to before, but cortisol increased later in pregnancy	Unreasonabl e to directly compare cortisol from 2nd vs. 3rd trimester due to physiologic increase over course of pregnancy	6
Rouse and Goodma n (2014)	N=77 (all with Hx of MDE prior to pregnancy; N=54 healthy pregnant women, N=23 depressed pregnant women)	Urine; RIA	Awakenin g until 1200	SCID	No association of cortisol and depression	Morning urinary collection for cortisol does not account for diurnal cortisol variation	8
O'Conno r et al. (2014)	N=101 (N=88 healthy pregnant women, N=13 depressed pregnant women)	Saliva; EIA	Cortisol x5 for CAR, at 20 and 32 weeks gestation	SCID (EPDS)	Depression negatively correlated with cortisol upon awakening followed by a higher level of cortisol later in the day	N/a	9
de Rezend e et al. (2016)	N=104 (N=37 depressed postpartu m women, N=42 healthy postpartu m women, N=25 healthy non-postpartu m women)	Saliva; RIA	Awakenin g, 1/2 hour, 3 hours, and 12 hours later at 6 months postpartu m	SCID (HDRS, EPDS)	Depressed PP women had significantly decreased cortisol at awakening, ½ hour and 3 hours after awakening; depressed PP women had significantly decreased cortisol at ½ hour after awakening compared to euthymic PP women	N/a	8

AUC area under the curve; *BDI* Beck Depression Inventory; *BIS* Behavioral Inhibition Scale; *CAR* cortisol awakening response; *CBSM* Cognitive Behavioral Stress Management; *CES-D* Centre for Epidemiological Studies Depression Scale; *Dx* Diagnosis; *EPDS* Edinburgh Postnatal Depression Scale; *EIA* enzyme immunoassay; *ELISA* enzyme-linked immunosorbent assay; *HDRS* Hamilton Depression Rating Scale; *Hx* History; *M-CIDI* Munich-Composite International Diagnostic Interview; *MDD* Major Depressive Disorder; *N/a* not applicable; *PES* Pregnancy Experiences Scale; *POMS* Profile of Mood States; *PP* Postpartum; *PPD* postpartum depression; *RIA* radioimmunoassay; *SCID* Structured Clinical inventory for DSM Disorders; *STAI* State-Trait Anxiety Inventory; *STAXI* State-Trait Anger Expression Inventory; *UC* Usual Care; *vs.* versus

*Deeks et al., 2003

Table 2

TSH in Peripartum Major Depression

Authors	Subjects	Methods	Depression scale(s)	Reported Outcomes	Limitations	NOS*
Abou-Saleh et al. (1998)	N=34 (N=30 healthy postpartum subjects, N=4 depressed postpartum subjects)	Serum TSH on day 7 postpartum, 0900–1000	PSE (EPDS)	No difference in TSH in depressed women	Sampling bias (<40% of original study population was willing to provide blood samples)	4
Kent et al. (1999)	N=748 (N=91 postpartum women with TSH or FT4 outside of reference range, N=387 postpartum women with normal TSH and FT4)	Serum TSH	GHQ28, CIDI-A, HDRS	High prevalence of postpartum thyroid dysfunction but no difference in depressive Sx; depression prevalence of 9.4%	N/a	8
Kuijpens et al. (2001)	N=291 (all pregnant women)	Serum TSH at 12 and 32 weeks gestation, then at postpartum weeks 4, 12, 20, 28, and 36	RDC by clinician interview for major or minor depression	TPOAbs were independently associated with depression at 12 weeks gestation, and at 4 and 12 weeks PP	Included Dx of both major and minor depression, with incidence >50%; authors concluded that study may have been underpowered	6
Lucas et al. (2001)	N=641 (all pregnant women)	Serum TSH (FT4, thyroperoxidase and thyroglobulin antibodies) at 36 weeks, then postpartum at 4 days, and 1, 3, 6, 9 and 12 months	DSM-III criteria (after BDI)	56 women developed PPTD; 61 women had BDI>21, but 11 were Dx with PPD (incidence 1.7%); however, none of the women with PPTD were Dx with PPD; women with past Hx of depression had greatest risk for PPD, while those who breastfed had lowest risk	Low prevalence of depression (1.7%)	6
Oretti et al. (2003)	N=238 (N=123 healthy pregnant women, N=115 pregnant women with positive thyroid antibody status)	Serum TSH (T3 and T4) at 16 weeks, then at 8, 12, 20, and 28 weeks postpartum	RDC assessment for depression at postpartum weeks 8,12, 20, and 28 (HDRS)	No association between PPD and any form of thyroid dysfunction; however, significant increase in mean of total and negative life events in women who met RDC criteria for MD independent of thyroid antibody status	N/a	8
Parry et al. (2003)	N=20 (N=2 healthy pregnant women, N=3 depressed pregnant women, N=2 healthy postpartum women, N=13 depressed postpartum women)	Serum TSH overnight every 30 min from 18:00 until 11:00	SCID (HRDS, BDI)	TSH acrophase occurred later in depressed women during pregnancy, but TSH acrophase occurred earlier in depressed postpartum women; TSH amplitude, however, was lower in depressed patients both during pregnancy and postpartum	Small sample size	5
Plaza et al. (2010)	N=103 (all women Dx with PPD within 6 months of parturition)	Serum TSH	SCID (HDRS, EPDS, Early Trauma Inventory Self Report)	No association between MD and thyroid hormone elevation or thyroid autoimmunity; childhood sexual abuse doubled the relative risk of MD in peripartum period	No healthy (non-depressed) comparison subjects	3

BDI Beck Depression Inventory; *CIDI-A* Composite International Diagnostic Interview; *DSM* Diagnostic and Statistical Manual; *Dx* Diagnosis; *EPDS* Edinburgh Postnatal Depression Scale; *GHQ28* General Health Questionnaire; *HDRS* Hamilton Depression Rating Scale; *MD* Major depression; *N/a* Not applicable; *NOS* Newcastle-Ottawa Score; *PP* Postpartum; *PPD* Postpartum Depression; *PSE* Present State Examination; *RDC* Research Diagnostic Criteria; *SCID* Structured Clinical Inventory for DSM Disorders; *Sx* Symptoms; *TD* Thyroid dysfunction; *TGAb* Thyroglobulin autoantibodies; *TPOAb* Thyroid peroxidase antibody; *TSH* Thyroid stimulating hormone

* Deeks et al., 2003

Table 3

Prolactin in Peripartum Major Depression

Authors	Subjects	Methods	Depression scale(s)	Reported Outcomes	Limitations	NOS*
Abou-Saleh et al. (1998)	N=34 (N=30 healthy postpartum subjects, N=4 depressed postpartum subjects)	Serum prolactin on day 7 postpartum, 0900–1000	PSE (EPDS)	Prolactin was lower in depressed postpartum women	Sampling bias (<40% original study population)	4
Parry et al. (2003)	N=20 (N=2 healthy pregnant women, N=3 depressed pregnant women, N=2 healthy postpartum women, N=13 depressed postpartum women)	Serum prolactin overnight every 30 min from 18:00 until 11:00	SCID (HRDS)	Prolactin was elevated in depressed women during pregnancy and postpartum	Small sample size	5
Okun et al. (2011)	N=56 (all pregnant women with Hx of MDD; randomized to N=20 nortriptyline, N=10 sertraline, N=26 placebo)	Serum prolactin postpartum at weeks 2, 3, 4, 6, 8, 11, 14, 17	clinician interview (HDRS)	No difference in prolactin in depressed women	High risk population recruited during pregnancy, with 20% who developed PPD; lack of repeated measures in same day	7

EPDS Edinburgh Postnatal Depression Scale; *HDRS* Hamilton Depression Rating Scale; *Hx* History; *MDD* Major Depressive Disorder; *NOS* Newcastle-Ottawa Score; *PPD* Postpartum Depression; *PSE* Present State Examination; *SCID* Structured Clinical Inventory for DSM Disorders

*Deeks et al., 2003