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The Relationship between Prenatal Stress, Depression, Cortisol and Preterm Birth: A Review

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Preterm birth is one of the most common adverse pregnancy outcomes. Maternal risk factors such as stress and depression have been associated with preterm birth. Preterm infants are at a higher risk of poor growth and neuro developmental outcomes. The objective of this paper is to examine the relationship between maternal stress, depression, cortisol level, and preterm birth. Preterm birth is one of the most common adverse pregnancy outcomes with a global prevalence of 9.6% and one of the major contributors to infant mortality and morbidity. The association between psychosocial stress and preterm birth, although examined for more than 25 years, has not yet been fully established. A systemic review was conducted in which research studies and review articles from 1970 to 2012, published in English, focusing on human subjects, and addressing the relationship between stress, depression, cortisol and preterm birth were included in this review. The studies examining the relationship between stress, cortisol levels and preterm birth have shown inconsistent findings that may be explained by varied study designs, differences in defining and measuring stress, timing of stress measurement, sample characteristics, and study designs. The relationship between stress, cortisol levels and preterm birth may be multifactorial and complex with premature birth being the final common pathway. A longitudinal cohort study, with a large sample size and multiple measures of stress, depression, and cortisol level, as well as a measure of anxiety and other stress hormone biomarkers may add new knowledge and enhance our understanding about the contribution of psychosocial stress to preterm birth.

Keywords: Maternal Stress; Antenatal Stress; Maternal Depression; Preterm Delivery; Preterm Birth; Gestational Age; Low Birth Weights; Cortisol

Introduction

Preterm birth, defined as "birth before 37 completed weeks" (Steer, 2005: p. 1), is one of the most common adverse pregnancy outcomes. Preterm birth is a global issue, irrespective of region or the level of resources (Beck et al., 2010). All resource regions: high, middle, and low report varying degrees of preterm birth rates (Beck et al.). The rate of preterm delivery ranges from 5% in developed countries to 25% in developing countries (Goldenberg et al., 2008; Steer, 2005). Africa (11.9%), followed by North America (10.6%) and Asia (9.1%) have the highest rates of preterm birth. The estimated global rate of preterm birth is 9.6% which is close to the rate of preterm birth rate in Asia (Beck et al.). Studies indicate that preterm birth has an impact on the rate of infant mortality and morbidity (Mathew & Mac Dorman, 2007). According to the World Bank (2008), the global infant mortality rate was 46 per 1000 live births. Prematurity and its complications account for almost 30 percent of neonatal deaths (Mathews & Mac Dorman). The cost of the hospitalization of preterm birth infant is $5.8 billion representing half of infant hospitalization cost (Russell et al., 2007). Moreover, stress of hospitalization and fear of losing an infant is traumatic and a source of grief for the family. Besides this, the psychological distress and risk of postpartum depression increases with having a preterm baby (Hill & Aldag, 2007). Preterm infants are also at a greater risk of serious health problems, such as cerebral palsy, blindness, breathing problems, and cognitive learning disabilities (Green et al., 2005; Latengresse, 2009; Rafati et al., 2005). Kramer et al. (2009) stated that understanding the etiology of preterm birth will facilitate early identification of mothers at risk for preterm birth. Implementation of early intervention strategies for these high risk mothers will decrease preterm birth thereby reducing the burden of preterm birth (i.e., infant mortality, morbidity, postpartum depression, parental role stress, and financial

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stress).

There are many maternal factors which are associated with preterm birth and these have been extensively highlighted in literature, such as low socioeconomic status, maternal age, and low level of education, anemia, inadequate prenatal care, psychosocial stress, obstetric complications, smoking, and maternal history of preterm delivery (Allen, 2001; Astolfi & Zonta, 1999; Hsieh et al., 2005; Ismail, Zaidi, & Maqbool, 2003; Mavalankar, Gray, & Trivedi, 1992). The relationship of many of these factors to preterm birth is clear. However, the association between psychosocial stress and preterm delivery, although examined for more than 25 years, has not yet been fully established (Dunkel-Schetter, 1998; Latendresee, 2009).

Stress and depression alters the hypothalamic-pituitary-adrenal (HPA) axis whereby corticotrophin-releasing-hormone (CRH) is secreted by the hypothalamus which in turn stimulates the pituitary gland to secrete adrenocorticotrophic hormone (ACTH). ACTH stimulates the adrenal cortex to secrete cortisol hormone (Diego et al., 2009; Giurgescu, 2009; Ruiz et al., 2001) and the adrenal medulla to secrete norepinephrine and epinephrine (Holzman et al., 2009). Increased cortisol levels further signal the hypothalamus and pituitary gland in a negative feedback loop to decrease CRH production. However, in depressed patients the negative feedback loop malfunctions resulting in excess production of CRH; hence cortisol. Simultaneously, stress alters the immune function and increases the production of cytokines. A negative feedback loop exists between the HPA axis and the immune system. Cytokines stimulate the HPA axis and lead to excessive secretion of cortisol (Behrman & Butler, 2007). In acute stress, glucocorticoids suppress the inflammatory process but in chronic stress glucocorticoids can enhance inflammation (Behrman & Butler). The increased secretion of CRH, ACTH, cortisol, and cytokines stimulate prostaglandin secretion which is responsible for the contraction and dilation of the smooth muscle, could lead to preterm labor and premature rupture of membrane. Therefore, changes in the hormonal milieu due to stress and depression may contribute to premature initiation of labor and preterm birth.

Given the high prevalence of psychological disorder in women during pregnancy (Bennett, Einarson, Taddio, Koren, & Einarson, 2004) preterm birth may be reduced by understanding the psychosocial risk factors associated with cortisol and preterm birth and developing intervention strategies to mitigate their impact. Cortisol levels may be a more objective measure of stress and depression thereby facilitate our understanding of the relationship between stress, depression and preterm birth. The purpose of this review was to critically examine the relationship between stress, depression, cortisol and preterm birth and identify gaps in the scientific literature.

Methods

A systematic and comprehensive search was undertaken to extract relevant articles on the relationship between maternal stress, depression, cortisol level, and preterm birth. The literature search was carried out through several electronic databases like Cumulative Index to Nursing and Allied Health (CINAHL), Science Direct, MD Consult and Blackwell Synergy from 1970 to 2011. Key words used to guide the search included maternal stress, antenatal stress, maternal depression, preterm delivery, preterm birth, gestational age, low birth weights and cortisol. The search was expanded to specific nursing and medical journals such as Journal of Midwifery and Women Health, Research and Health, Journal of Obstetrics, Gynecology and Neonatal Nursing, American Journal of Obstetrics and Gynecology, and Lancet and American Journal of Epidemiology as they are the most relevant sources for new knowledge in maternal and child health. Also, the reference lists of all relevant articles were reviewed to identify additional articles. Articles were included if they examined the relationship between stress or depression, cortisol level and preterm birth.

Findings

Overview of the Included Studies

A total of 49 articles were found examining the relationship between stress, depression, cortisol and preterm birth. Of these, 27 articles were excluded as they focused on infant cortisol level, non-pregnant women, fetal cortisol, and birth weight of the infant rather than examine the relationship between the variables of interest. Therefore, a total of 22 articles were selected for the review as given their focuses on the relationship between stress, depression, cortisol and preterm birth (see **Figure 1**). Although everal studies have attempted to understand the psychosocial risk factors associated with preterm birth, the relationships examined have varied between studies. For instance, a number of researches examined the relationship between stress, depression and preterm birth without considering cortisol (Copper et al., 1996; Dole et al., 2003; Jesse, Swanson, Newton, & Morrow, 2009; Jesse, Seaver, & Wallace, 2003; Wadhwa, Culhane, Vitgina, Brave et al., 2001; Khashan et al., 2009; Whitehead et al., 2002; Zhu et al., 2010). Two studies examined the relationship between stress and cortisol only (Harville et al., 2009; Obel et al., 2004) while five studies only explored the relationship between cortisol and preterm birth (Campbell, Challis, DaSilva, & Bocking, 2005; Phocas, Sarandakou, & Rizos, 1990; Mazor et al., 1994, 1996; Sandman et al., 2006). Of the 22 articles seven determined the relationship between stress or depression,

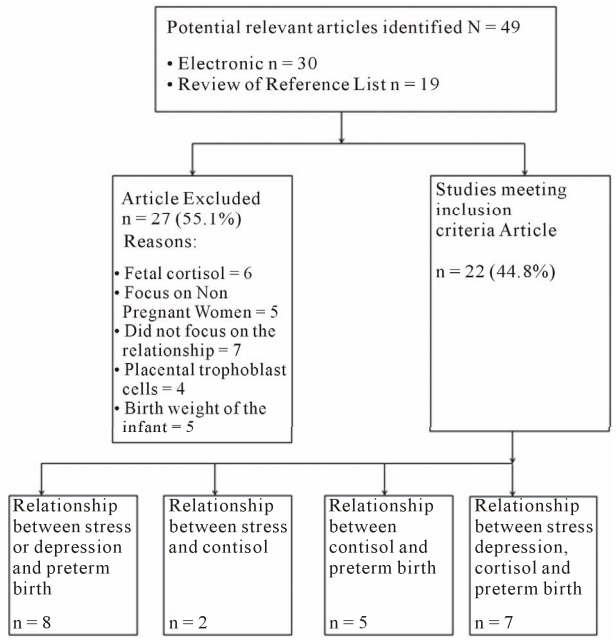

Figure 1.
Flow of studies from initial screening to inclusion.

cortisol and preterm birth together at the same time (Diego et al., 2009; Erickson et al., 2001; Field et al., 2004, 2006; Hobel et al., 1999; Kramer et al., 2009; Shaikh et al., 2011).

Relationship between Prenatal Stress or Depression and Preterm Birth

Many studies demonstrate an association between stress and preterm birth (Copper et al., 1996; Erickson et al., 2001; Hobel et al., 1999; Jesse et al., 2009; Ruiz et al., 2001). Copper et al., in a prospective study, enrolled 2593 pregnant women between 25 to 29 weeks of gestation and demonstrated that stress was significantly associated with spontaneous preterm birth and low birth weight. Similarly, Jesse et al. (2003) conducted a prospective correlation research design in which 120 Appalachian pregnant women were recruited between 16 and 28 weeks of gestation and showed that symptoms of depression, level of self esteem, and perception towards pregnancy were significantly associated with preterm delivery. Women with depressive symptoms were four times more likely to deliver preterm birth as compared to women without depressive symptoms. In this study the rate of preterm delivery was 27 out of 120 babies (i.e., 23% delivered preterm). Also, a population based retrospective cohort study conducted in Denmark between January 1979 and December, 2002, reported that maternal exposure to severe life events increased the risk of preterm delivery (Khashan et al., 2009). Whitehead, Hill, Brogan, and Blackmore-Prince (2002) explored that stress beyond a certain threshold affects the relationship between stress and preterm birth.

On the other hand, many studies have reported contradictory findings. Jesse et al. (2009) studied the relationship between biopsychosocial factors and preterm birth in different ethnic groups. Preterm delivery was three times higher in African American than Hispanic and Caucasian women, but there was no significant relationship between depressive symptoms and preterm birth in African American or Caucasian women. Many other studies have emphasized racial disparity as one of the causes of preterm birth and highlighted that preterm birth was more evident in African-American women compared to non-Hispanic white women (Kramer & Hogue, 2009; Pearl, Braveman, & Abrams, 2001).

Wadhwa et al. (1993) also used a prospective study and recruited 90 women at 22 and 28 weeks of pregnancy and showed no significant relationship between perceived stress and gestational age at birth. In addition, Dole et al. (2003) reported similar findings in which life events, social support and depression were not significantly associated with preterm birth. Similarly, Hedegaard, Henriksen, Secher, Hatch and Sabroe (1996) in a population based study of 5873 pregnant women reported that negatives life events during pregnancy did not increase the risk of preterm birth.

Relationship between Stress and Cortisol

Harville et al. (2009) analyzed data of stress and cortisol from 1587 North Carolina and collected one saliva sample for cortisol measurement and blood for CRH at 14 - 19 and 24 - 29 weeks' gestation and found no co-relation between self-reported indicators of stress and hormones such as cortisol and corticotrophin-releasing hormone. While Obel et al. (2005) examined the exposure to stressful life events and changes in levels of cortisol during pregnancy in a population of 603 pregnant women and found evening cortisol to be more strongly associated with stress markers than morning cortisol.

Relationship between Cortisol and Preterm Birth

High cortisol level in pregnancy has been associated with adverse pregnancy outcomes like aborted fetus, delayed fetal growth, preterm delivery, and low birth weight baby (Campbell, Challis, DaSilva, & Bocking, 2005; Field, Diego, Hernandez-Reif, et al., 2008). A systematic review has been done to determine the relationship between cortisol levels and preterm birth (Giurgescu, 2009). For this review, fifteen studies were selected. Out of these, some studies determine the relationship of cortisol and preterm birth and the remaining studies determine the relationship of maternal stress, depression, anxiety, cortisol, and preterm delivery. The majority of these studies suggested that women with higher cortisol levels in pregnancy were at greater risk of preterm birth. Phocas et al. (1990) measured maternal cortisol levels in 204 pregnant women at different gestational ages. The blood cortisol samples were obtained between 8:00 a.m. to 9:00 a.m. Cortisol gradually increased from 6 weeks to 40 weeks of pregnancy and a sharp rise was noted two weeks before the onset of labor in normal pregnancy.

Mazor et al. (1994) measured the amniotic fluid and plasma concentrations of cortisol in 38 women with preterm labor and intact membrane between 32 and 36 weeks of gestation. Maternal plasma cortisol levels were significantly higher in women with preterm births than in those who delivered at term, but no significant differences were reported in amniotic fluid cortisol concentration. Similar results were found in a study where plasma and amniotic fluid cortisol were measured for 40 pregnant women with preterm labor and intact membrane at 28 to 30 weeks of gestation (Mazor et al., 1996).

Sandman et al. (2006) studied the relationship between maternal cortisol and CRH in 203 pregnant women in a longitudinal study. Cortisol at 15 weeks of gestation predicted elevated CRH at 31 weeks. A few studies measured the blood cortisol level in pregnant women admitted with a diagnosis of threatened preterm labor (Campbell et al., 2005). Cortisol was significantly higher in women who gave birth within 24 to 48 hours of hospitalization. A majority of results of these studies lend support to the premise that high blood level of cortisol increases the risk of preterm delivery.

Relationship between Stress or Depression, Cortisol and Preterm Birth

The studies that examine the relationship between maternal stress, cortisol and preterm birth together at the same time have inconsistent findings (see **Table 1**) (Erickson et al., 2001; Hobel et al., 1999; Kramer et al., 2009; Ruiz et al., 2001; Shaikh et al., 2011). Few studies (Erickson et al., 2001; Hobel et al., 1999; Kramer et al., 2009) support the hypothesis that cortisol levels increase with maternal stress. However, the Ruiz et al. (2001) study does not support the hypothesis that cortisol levels increases with stress, but it shows a significant relationship between stress and gestational age. Moreover, Shaikh et al. (2011) did not find any relationship between stress, cortisol and preterm birth.

Erickson et al. (2001) prospectively recruited 3596 women and matched 59 women who delivered preterm with 300 women who delivered at term. Hobel (1999) also conducted a prospective study in which 524 women of diverse ethnic and

Table 1.
Relationship between prenatal stress, cortisol, and preterm birth.

Study	Design	Participants	Scales	Specimen	Time Period of measurement	Result
Erickson et al. (2001)	Prospective cohort study design	3596 pregnant women	Questionnaire I: Previous and present medical history. Questionnaire II: Social and demographic information. Questionnaire III: Present urogential and obstetric problems.	Blood	7 - 23 and 27 - 37 weeks of gestation and at 37 - 43 weeks of gestation for those who delivered at term.	Mean cortisol levels were higher in women who delivered preterm at 27 - 37 weeks of gestation. 27 - 37 weeks: Cortisol levels were higher in the preterm group as compared to the term group.
Hobel et al. (1999)	Case control study design	524 pregnant women 18 preterm patients were matched with 18 term patients.	PSS, SSAI	Blood	18 to 20 weeks, 28 to 30 weeks and 35 to 36 weeks of gestation	Patients who delivered preterm had significantly elevated cortisol levels at 18 to 20 weeks' gestation and 28 to 30 weeks' gestation.
Kramer et al. (2009)	Prospective cohort study nested case control analysis	5337 pregnant women	Demographic questionnaire, daily hassles scale, marital strain scale of pearlin and schooler, abuse assessment screen, arizona social support interview schedule, perceived stress scale, dunkel-schetter scale, rosenberg self esteem scale, and CES-D	Hair	24 - 26 weeks of gestation	Pregnancy related anxiety and depression were associated with preterm birth. Hair cortisol was positively associated with gestational age but not CRH. Maternal plasma CRH, hair cortisol, and placental histopathologic of infection were not associated with stress, anxiety, or distress measures.
Ruiz et al. (2001)	Prospective longitudinal observational study design	78 pregnant women	PSS	Blood, vaginal swabs	15 - 19, 20 to 22, 23 - 26, 27 - 30, and 31 - 35 weeks of gestation	Cortisol concentration did not correlate with gestational age at birth. The change in PSS scores was significantly related to gestational age at birth.
Shaikh et al. (2010)	Prospective cohort study design	143 pregnant women	A-Z stress scale, CES-D scale	Blood	28 weeks of gestation	There were no significant relationship found between stress, depression, cortisol and preterm birth.

socioeconomic background were followed till delivery but only 18 women who delivered preterm were matched with 18 women who delivered at term. Moreover, Kramer, Lydon, et al. (2009) prospectively recruited 5337 pregnant women of Montreal and conducted a nested case-control study. But, Ruiz et al. (2001) conducted a prospective, longitudinal, observational study in which 78 women were recruited and followed till delivery and divided into three groups: normal term (n = 53), preterm labor (n = 17), and preterm birth groups (n = 6). Shaikh (2011) conducted a prospective cohort study in which 132 women were recruited between 28 - 30 weeks of pregnancy and followed till delivery.

Erickson et al. (2001) reported women with preterm birth had higher cortisol levels at 27 - 37 weeks of gestation, but no increase was reported at 7 - 23 weeks. Education level and work related variables (walking more than 6 hours a day, working more than 42 hours a week) were strongly associated with preterm delivery. Moreover, Hobel et al. (1999) concluded that the preterm group had higher cortisol levels at 18 to 20 weeks and 28 to 30 weeks, but not at 35 to 36 weeks. In addition, Kramer et al. (2009) concluded that among multiple stress measurements, pregnancy related anxiety, perception of high pregnancy risk, and depression were associated with preterm birth. Hair cortisol was positively associated with gestational age but CRH was not. In contrast, Ruiz et al.'s (2001) study does not support the hypothesis that cortisol levels increases with stress, but it shows a significant relationship between stress and gestational age. Also, Shaikh (2011) study showed no significant relationship between stress, cortisol, and preterm birth.

A few studies have been carried out to identify the relationship between maternal depression, cortisol levels, and preterm delivery and these show a significant relationship between the three variables (see **Table 2**) (Diego et al., 2009; Field et al., 2004, 2006; Field, Diego, Hernanzer-Rief et al., 2008). Field et al. (2004) compared 70 pregnant women with and without depression at 20 weeks of gestation by using the CES-D. The study findings showed a significantly greater number of premature births in depressed women as compared to non-depressed women (25% versus 7%, $P < 0.01$).

Field et al. (2006) recruited 300 pregnant women at 20 weeks of gestation and their urinary cortisol levels were collected at mid morning. The incidence of preterm was significantly higher in the group with high cortisol level. Diego et al. (2009) conducted a study in which 40 depressed and 40 non-depressed women were recruited on the basis of their CES-D score, which was measured in 18 and 20 weeks of gestation. The findings suggested that depressed mothers had a 13% higher incidence of preterm birth. Also, depressed women had more elevated prenatal cortisol levels than non-depressed women.

A study of 430 pregnant women, chronic prenatal depression and cortisol levels were assessed longitudinally at 22 and 32 weeks of gestation (Field, Diego, Hernandez-Reif et al., 2008).

Table 2.
Relationship between prenatal depression, cortisol, and preterm birth.

Study	Design	Participants	Scales	Specimen	Time period of measurement	Results
Field et al. (2004)	Prospective longitudinal study design	70 pregnant women with depression and 70 without depression	CES-D scale, STAI, profile mood states, anger scale, vagal tone, EEG asymmetry and neonatal behavior during sleep and during the brazelton neonatal behavior assessment scale	Maternal and neonatal urine for cortisol, dopamine, and serotonin	20 weeks of gestation and within 24 hours of delivery	The study findings showed significantly greater number of premature births in depressed women as compared to non-depressed women (25% versus 7%, $P < 0.01$). Cortisol was a significant predictor of preterm birth.
Field et al. (2006)	Prospective cohort	300 pregnant women	CES-D, structured clinical interview of diagnosis, STAI and STAXI, behaviour inhibition, and behaviour approach system questionnaire, neonatal assessments	Urine cortisol	20 weeks of gestation	The high cortisol group had higher CES-D scores. The fetus was more active and had a smaller head circumference, abdominal circumference, biparietal diameter, less fetal weight and a shorter gestational age.
Diego et al. (2009)	Prospective cohort study	40 depressed and 40 non-depressed pregnant women	Schedule of recent life events, daily hassles, perceived stress scale, hopkins symptom checklist, and pregnancy-related anxiety	Urine cortisol	18 - 20 weeks of gestation (i.e., mid gestation)	Depressed women had a 13% greater incidence of premature delivery than non-depressed women. Depressed women also had elevated prenatal cortisol levels than non-depressed women.
Field, Diego, Hernandez-Reif et al. (2008)	Prospective longitudinal study design	430 pregnant women	SCID, CES-D, STAI and STAXI, Daily hassles and urine cortisol		22 weeks and 32 weeks of gestation	The depressed group had a higher cortisol levels as compared to the non-depressed group on the first prenatal visit but no difference in cortisol level was noted on the second visit. The depressed group had a higher rate of preterm birth than the non-depressed group.

ACTH Adrenocorticotrophic Hormones, CBC Complete Blood Count, CRH Corticotrophin-releasing-hormones, ACTH Adrenocorticotrophic Hormones, PSS Perceived Stress Scale, SSAI The Spielberger State Anxiety Inventory, CES-D Centre for Epidemiology Studies Depression Scale, CRH Corticotrophin-releasing-hormones, STAI State Anxiety Inventory, EEG Electroencephalography, STAXI State Anger Inventory, SCID Structured Clinical Interview for DSM IV Disorder.

After delivery, postnatal depression was assessed and the relationship with neonatal outcomes was assessed.The depressed group had higher cortisol levels as compared to the non-depressed group on the first prenatal visit but no difference in cortisol levels was noted on the second visit in the two groups. The depressed group had more incidences of preterm birth than the non-depressed group. Hence, all these studies highlight the significance of maternal cortisol as an important predictor for preterm delivery and an indicator of depression.

Discussion

The existing literature on the relationship between stress, depression, cortisol and preterm does not have a common, clear, and consistent definition of the concept of stress, as evident from the different measures of stress (i.e., the various scales) used. The researchers have used a variety of scales to measure stress which makes it difficult to compare the results. For instance, Whitehead et al. (2002) measured stress by negative life events, which included family illness, death, finances, job loss, relationships, physical injury, and legal matters, whereas Hobel et al. (1999) measured the perception of stress by using the PSS and Spielberger State Anxiety Inventory (STAI). Erickson et al. (2001) study included previous and present medical history, stressful life situations, and questions on behaviors, and present urogenital and obstetric history. Ruiz et al. (2001) used only the PSS. In addition, Wadhwa et al. (1993) assessed stress using multiple scales, such as Schedule of Recent Life Events, Daily Hassles Questionnaire, PSS, Hopkins Symptoms Checklist for measuring psychological and physical symptoms and Pregnancy Related Anxiety Scale. Obel et al. (2005) and Zhu et al. (2010) used Life Events Checklist. Shaikh et al. (2011) used A-Z stress scale. Moreover CES-D was used to assess depression (Diego et al., 2009; Field et al., 2004, 2006; Shaikh et al., 2011). The varied variables for instance live events, daily hassles, social support used in different studies to assess stress during pregnancy makes it difficult to compare the outcomes as varied measures are used. There has been no universal standard method to measure stress in pregnant women. The lack of use of a standardized scale to measure stress contributes to the inability to confirm the association between maternal stress, cortisol level and preterm birth (Lantendresse, 2009; Paarlberg et al., 1995).

The different inclusion and exclusion criteria used in studies may also explain the inconsistent findings. Erickson et al. (2001); Harville et al. (2009); Hobel et al. (1999); Kramer et al. (2009); Obel et al. (2003); Shaikh et al. (2011) and Zhu et al. (2010) enrolled primiparous and multiparous women, while Ruiz et al. (2001) enrolled only primiparous women. In addition, a few studies excluded women who received betamethasone (Erickson et al.; Hobel et al.; Mazor et al., 1994, 1996; Shaikh et al.) whereas Harville et al.; Kramer et al.; Obel et al. (2003) and

Ruiz et al. (2001) did not mention betamethasone treatment. Betamethasone affects the cortisol level and therefore may not highlight the relationship between stress, cortisol, and preterm delivery. Moreover, a few studies excluded women with diabetes mellitus, thyroid disorder, and chronic renal or heart disease and uterine and cervical abnormalitywhich are the risk factors for preterm birth and can impact the result (Diego et al., 2009; Kramer et al.; Ruiz et al.; Shaikh et al.; Zhu et al.).

Cortisol undergoes diurnal variation. It is at its highest prior to awakening and decreases during the day and is at its lowest in the evening (Levine et al., 2007; Ruiz et al., 2001). Therefore, cortisol should be drawn in the morning or the afternoon, consistently, for each subject. Hobel et al. (1999) collected plasma cortisol level between 9 a.m. to 1 p.m. Harville et al. (2009) collected between 8 a.m. and 10 a.m. while Ruiz et al. (2001) collected plasma cortisol either in the morning or the afternoon, consistently, for each subject. Obel et al. (2005) collected morning and evening sample. A number of studies collected first morning urine cortisol sample (Diego et al., 2009; Field, 2004, 2006). The different time periods in which stress and depression were measured may explain the variation in findings regarding the link between stress, depression, and preterm birth. Paarlberg, Vingerhoets, Passchier, Dekker, and Geijn (1995) observed that an identical stressful condition led to different effects depending on when during the pregnancy (i.e., which trimester) the stressful condition occurred whereas in late pregnancy the same stimuli can lead to preterm delivery. In their view stress in early pregnancy affects the developing fetus. The use of a longitudinal design, where multiple measurements are taken, will give a better understanding of the relationship between stress and preterm delivery (Giurgescu, 2009).

On the other hand, the Erickson et al. (2001) study collected serum cortisol but did not mention the time the sample was collected. The varied times of data collections may also explain the inconsistent findings. Some studies used blood (Erickson et al., 2001; Phocas et al., 1990; Hobel et al., 1999; Mazor et al., 1994, 1996; Ruiz et al., 2001) to measure the cortisol level whereas a few studies measured cortisol in urine (Diego et al., 2009; Field et al., 2004, 2006) and one study used hair to measure cortisol (Kramer, et al., 2009) and two studies used saliva (Harville et al.; Obel et al.). Cortisol levels can be detected in blood, urine, and saliva. Urinary cortisol is a non-invasive procedure and a better way to measure cortisol than other measures for frequent and rapid sampling. Levine et al. (2007) explained the reason for preferring 24 hours urine sample for cortisol as "Urinary cortisol excretion results from glomerular filtration and is a useful index of integrated 24 hours plasma free cortisol" (p. 46). Therefore, urinary cortisol may be a more accurate measure of maternal cortisol levels when a 24 hours urine collection for cortisol is taken rather than a single measure of urine for cortisol (Levine et al.).

The studies examining the relationship between stress, cortisol levels and preterm birth, shows inconsistent results. Some studies (Hobel et al., 1999; Erickson et al., 2001; Kramer et al., 2009) support the relationship between stress, cortisol, and preterm births, whereas others (Ruiz et al., 2001; Harville et al., 2009) found cortisol to be a poor biomarker. In normal pregnancy, the cortisol level increases throughout pregnancy and at mid pregnancy the level increases by 50% due to the production of CRH via placenta (Ruiz et al., 2001). Measuring stress once in a pregnancy may not provide an adequate appraisal of the psychosocial health of the women throughout the pregnancy. Hence, multiple measurements of stress variables are likely to provide a more in-depth understanding of the relationship between stress and preterm birth. Even though there are inconsistencies in the findings of the studies that address the relationship between stress, depression, cortisol, and preterm birth, high levels of cortisol may be one of the strong biomarkers for preterm delivery (Giurgescu, 2009). In other words, higher stress and depression scores and higher levels of cortisol when occurring together, may predict preterm birth. The relationship between stress, depression, cortisol levels and preterm birth may be multifactorial and complex with premature birth being the final common pathway.

Implications for Research

Studies (Field et al., 2004, 2006; Field, Diego, Hernandez, et al., 2008) suggest that among pregnant women cortisol gets elevated with co-occurring anxiety and depression. Hence, adding an anxiety measure would enhance the psychological measures and allow for more sophisticated data analyses, such as comparing women with elevated scores on both anxiety and depression. Furthermore, a recent study by Holzman et al. (2009) proposed other biomarkers, such as catecholamine level (e.g., epinephrine, norepinephrine, and dopamine) for preterm delivery. Therefore, adding this biomarker in future studies may contribute to our understanding of the mechanism responsible for preterm birth. Moreover, such studies should be done using non-invasive methods to check cortisol hormone like saliva because it is easier and painless if multiple measures are going Finally, a longitudinal cohort study design should be undertaken in which stress, depression and cortisol are measured in each trimester.

Implications for Practice

Mental health of pregnant women is often not given priority. Medical and Nursing clinicians (e.g., community health nurses) and lady health visitors should integrate assessment of psychosocial factors as standard of care provided to pregnant women. Early identification of stress and depression will permit the medical and nursing clinicians to implement measures to reduce stress and depression caused by psychological factors and its potential negative consequences such as preterm birth (Latendresse, 2009). Decreasing the incidence of preterm birth may reduce infant which is an important fourth millennium development goal. In addition, nurses should be educated about the importance of the psychological aspect of care. Group prenatal care may be one of the strategies nurses can employ to reduce stress (Field & Diego, 2008). Ickovics et al. (2007) demonstrated that group prenatal care which includes physical assessment, education and skills building, and support through facilitated group discussion, reduced the incidence of preterm birth when compared to women who received individual prenatal care. Group prenatal care reduced the stress and the effects on maternal and fetal endocrine stress response, minimizing the incidence of preterm birth.

Health professionals (e.g., physicians, nurses and psychologist) who have skills need to intervene in a timely way in order to lower the stress of pregnant women and to monitor the impact of their interventions to ensure that appropriate outcomes are attained. A number of interventions have been shown to reduce stress, anxiety and depression or its negative consequen-

ces including music therapy (Chang, Chen, & Feng, 2007), yoga (Narendran, Nagarathna, Narendran, Gunasheela, & Nagendra, 2005) and massage (Field et al., 2005).

The impact of interventions directed at reducing or managing stress thereby reducing the rate of preterm births needs to be evaluated. Those health providers who do not have expertise should make appropriate referrals to the psychologist.

Conclusion

Preterm birth is one of the most common adverse pregnancy outcomes and it is associated with infant mortality. Stress and depression stimulate HPA axis which enhance cortisol secretion increasing the risk of preterm birth. The relationship between stress, depression, cortisol level and preterm birth remains unclear. The studies discussed in this paper are in partial agreement that stress, depression and cortisol levels may contribute to preterm birth. Therefore, health care provider should assess psychological indicators more closely to provide appropriate treatment. A longitudinal cohort study, with multiple measures of stress, depression, and cortisol level, as well as a measure of anxiety and other stress hormone biomarkers may add new knowledge and enhance our understanding about the relationship between stress, depression, anxiety, cortisol level and preterm birth.

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