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MATERNAL CRH AND THE USE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS INDEPENDENTLY PREDICT THE OCCURRENCE OF PRETERM BIRTH

G Latendresse and

University of Utah College of Nursing, Salt Lake City, UT, USA

RJ Ruiz

University of Texas Health Science Center at San Antonio, School of Nursing, USA

Abstract

BACKGROUND—Studies support the premise that chronic maternal stress may trigger a premature sequence of physiologic events ending in preterm birth (PTB). Furthermore, chronic stress is highly correlated with depression and anxiety, which are also associated with PTB. However, some studies report that medication status rather than depression and/or anxiety may reflect the risk for PTB.

OBJECTIVE—While the purpose of this small preliminary study was to evaluate the association between chronic maternal stress and PTB, this report focuses on the unexpected finding of the association between maternal use of selective serotonin re-uptake inhibitors (SSRIs), and PTB.

METHODS—A prospective cohort study of 100 pregnant women included measures of contributors to chronic maternal stress, and corticotropin-releasing hormone (CRH). Demographic and behavioral data included smoking, substance use, and use of medications for depression and anxiety.

RESULTS—Pregnant women who used SSRIs to treat depression and/or anxiety were nearly 12 times more likely to deliver preterm when compared to women who did not use these medications. Women with CRH levels in the 4th quartile were 6 times more likely to deliver preterm when compared to women whose CRH levels were in the lower three quartiles. No associations were found between SSRI use and CRH levels.

IMPLICATIONS—Associations between preterm birth and maternal use of SSRIs are not understood. It is important not to alter current approaches to the treatment of depression and anxiety without thorough discussion with women regarding the potential benefits and harms of various treatment options.

Keywords

Preterm Birth; Pregnancy; Selective Serotonin Re-uptake Inhibitors; Corticotrophin-Releasing Hormone; Depression; Anxiety

INTRODUCTION

Nearly half of all preterm birth (PTB) is idiopathic, spontaneous, and predominantly related to psychosocial factors widely thought to contribute to maternal chronic stress.¹ There is

compelling evidence that for some women, chronic maternal stress may prematurely trigger the physiologic events that lead to birth.^{2–5} Furthermore, many chronic stress contributors, such as depression, anxiety, low social support, negative life orientation, and perceived stress are highly intercorrelated and nearly impossible to disentangle. While the purpose of this prospective cohort study was to investigate the associations between measures of chronic stress contributors and PTB, the results unexpectedly revealed an association between maternal use of selective serotonin reuptake inhibitors (SSRIs) for depression and anxiety disorders and PTB. The study used a biobehavioral approach to evaluate measures of psychosocial, demographic, and behavioral factors that may contribute to chronic stress, and included one biological marker (corticotrophin-releasing hormone – CRH) relevant to the pathophysiology of preterm birth. The aims of the study were to 1) evaluate the relationships between measures of chronic stress contributors at 14–20 weeks gestation and the outcome of PTB, and 2) determine which measures provided predictive value for PTB. A long-term goal of this research is to identify at-risk groups of women who could be targeted for interventions in future investigations.

BACKGROUND

Preterm birth, defined as birth that occurs prior to 37 completed weeks of pregnancy, is the major contributor to infant morbidity and mortality, and often has serious long-term health consequences, such as cerebral palsy, blindness, and developmental difficulties.^{6–7} No single causation has been identified, and there is general agreement that PTB has a multiplicity of contributors.^{1–2, 8} There is a fairly clear understanding of and approach to the management of mechanical and medical contributors to the occurrence of preterm birth (i.e., multiple gestation, placental abruption, polyhydramnios, infection), as well as medically induced PTB (i.e., due to placental insufficiency and severe pregnancy induced hypertension).⁹ However, the mechanisms involved in the *psychosocial* associations with *spontaneous* PTB are much less clear. The psychosocial factors most frequently associated with PTB include chronic and catastrophic stress and trauma, emotional responses and affective states (anxiety and depression), racism, low social support, lack of personal resources, and “intendedness” of pregnancy.² Furthermore, young age, being single, and low socioeconomic status have well-known associations with PTB. While many of these psychosocial factors obviously contribute to consequential health-related behaviors (e.g. smoking, poor nutrition, inadequate access to health care, substance abuse), research suggests that prolonged exposure to stress confers risk independent of such behaviors, possibly due to activation of stress response systems².

Indeed, several studies indicate that activation of the maternal and fetal hypothalamic-pituitary-adrenal (HPA) axes and the autonomic nervous system interacts with pregnancy and birth physiology to contribute to the occurrence of PTB.^{2, 3, 5, 10–17} These studies support the premise that *chronically* activated HPA and autonomic nervous system responses may trigger a premature sequence of physiologic events that culminates in PTB. The signals that initiate the normal physiologic birth process become prematurely activated via HPA and autonomic nervous system mediators (i.e. cortisol, adrenocorticotropin-releasing hormone – ACTH, vasopressin, catecholamines).^{18–20} These mediators are known to upregulate the production and secretion of placental corticotropin-releasing hormone CRH, a prominent peptide in the cascade of events leading to birth. The production of CRH is associated with the fetal adrenal production of dehydroepiandrosterone – sulfate (DHEA-S), and subsequent cervical and membrane degradation/remodeling, and gap-junction changes in uterine myometrial cells.^{18–20} As noted, central to this sequence in stress-related PTB is the precocious and/or exaggerated production and secretion of placental CRH, which otherwise has a known normal trajectory, first measurable in maternal blood between approximately 16–20 weeks of gestation.^{21–22} Normally, placental CRH

production increases steadily throughout pregnancy and culminates in its highest measurable levels during the last 6 weeks prior to birth, and has been referred to as the “placental time clock” for labor initiation.²³

Several psychosocial contributors to a chronically-activated and/or dysregulated stress response have been identified, including depression, anxiety, perceived stress, lack of social support, low socioeconomic status, and coping skill/style.^{24, 25} Moreover, several studies have found associations between psychosocial and chronic stress contributors and increased maternal CRH levels during pregnancy.^{5, 13, 14, 16, 17, 26, 27} The proposed pathway in these associations involve complex interactions between the maternal/fetal HPA and ANS activation and the physiology of pregnancy and birth.^{3, 20, 28, 29} Figure one depicts a proposed biobehavioral pathway that leads to PTB when the stress response systems are chronically activated in a genetically susceptible woman and/or fetus. Figure one provides a sampling of factors that may contribute to activation of the stress response; an all-inclusive list would be impossible to construct. It is important to note that the experience of “stress” is highly variable from individual to individual, reflecting the contribution of genetics, a lifetime of exposure to “stressors,” and personal appraisal and availability of resources (internal and external).³⁰ These are unique to each individual and account for the daunting and difficult task of measuring “chronic stress” in a standardized and clinically meaningful manner. This has led to a suggested research approach that includes multiple stress measures to more adequately capture the phenomenon in relation to pregnancy outcomes.³¹

There has been recent research interest in depression, anxiety, and antidepressant use, in relation to PTB. However, these recent studies have had conflicting results. ^{32–36} For example, in a prospective cohort study of 681 French women at 20–28 weeks gestation, Dyan et al found associations between PTB and depression scores, but did not establish medication status.³³ In another prospective cohort study of 300 women in Florida (50% Hispanic, 25% African-American, 20% Non-Hispanic White, 5% Asian), Field, et al reported that maternal cortisol levels had a stronger association with PTB than did depression scores, but this study also failed to indicate medication status.³⁴ In another study of 90 women primarily attending the UCLA obstetrics clinics, Suri, et al compared depressed pregnant women who took antidepressants to those who did not, and found that 7 out of 8 of the PTBs occurred in the mothers who were taking medication.³⁷ A Swedish study interviewed 1,465 women prior to 20 weeks gestation, evaluated them for mental disorders, and collected birth outcomes. These researchers found no association between PTB and depression and anxiety, but noted that *all* the women in the study who were taking antidepressants immediately stopped as soon as they became aware of the pregnancy.³²

The largest study to date, conducted in Denmark, evaluated the outcomes for 57,000 women and reported that women who were exposed to SSRIs during pregnancy were twice as likely to have PTB than those who did not, and with or without a history of psychiatric condition. ³⁸ However, it must be noted that only 329 women in that study reported such exposure during pregnancy, which is only ½ of 1% of the sample and is quite divergent from the 10–12% of U.S. women who are exposed during pregnancy. Furthermore, no measures of depression and/or anxiety were included in the Denmark study, which obscures our understanding of those results. It is not clear whether women in Scandinavian countries have a lower prevalence of depression/anxiety or if they are much less likely to utilize pharmacotherapeutics.

One notable study indicated an equal risk (20%) of PTB whether depressed pregnant women were untreated or pharmacologically treated.³⁶ This study, conducted at the University of Pittsburgh, recruited women from community prenatal clinics and included evaluation of differences between 5 groups: 131 women who had no depression or anxiety and took no

SSRIs; 48 women who had continuous SSRI exposure throughout pregnancy; 14 women with major depression during the entire pregnancy, but no SSRI exposure; 23 women who had partial exposure to SSRIs during at least one trimester of pregnancy; and 22 women who experienced major depression for only part of their pregnancy, without SSRI exposure.

The study reported here focused on several known or suspected psychosocial contributors to chronic stress, including depression and anxiety, in conjunction with a relevant biological marker in pregnancy, CRH. The purpose of this preliminary study was to evaluate the associations between chronic maternal stress and PTB, but the report will primarily focus on the unexpected finding of the association between maternal use of SSRIs and spontaneous, idiopathic PTB.

METHODS

Sample and Setting

The study was reviewed and approved by the Institutional Review Board of the University of Utah prior to study commencement. Pregnant women were recruited and enrolled from three community prenatal clinics from March through November, 2007, in collaboration with the University of Utah Health Research Network. These clinics serve a diverse population in the metropolitan area, and were specifically chosen in an attempt to obtain a representative sample that reflects the surrounding population.³⁹ Women, who were less than 20 weeks of gestation, at least 18 years of age, and spoke English, were invited to participate in the study. Women were excluded if they had a history of hypertension, diabetes, cardiovascular disease, immune disorders, autoimmune disorders, or systemic corticosteroid therapy. Women were also excluded for occurrences of threatened abortion, vaginal bleeding, or multiple gestation in the current pregnancy.

Measures

Between 14 and 20 weeks of pregnancy (verified by ultrasound examination prior to 20 weeks of gestation), the following measures were obtained: 1) maternal serum CRH levels via radioimmunoassay, 2) Center for Epidemiological Studies Depression Scale (CES-D),⁴⁰ 3) Perceived Stress Scale (PSS),⁴¹ 4) Life Orientation Test Revised (LOT-R; a measure of optimism vs. pessimism),⁴² 5) Brief Cope Scale (a measure of coping style),⁴³ 6) Pregnancy Specific Anxiety Scale (PSA),⁴⁴ and 7) Norbeck Social Support Questionnaire (NSSQ),⁴⁵ in addition to demographic and behavioral questions addressing tobacco, alcohol, and substance use, sleep, physical activity, and nutrition patterns, domestic violence, and use of medications for mental health conditions (i.e. depression and anxiety). These measures were selected based primarily on sound theoretical underpinnings, previous studies which indicated instrument effectiveness for evaluating contributors to the experience of chronic stress during pregnancy, and on the need to control for known confounding variables (i.e. smoking, age, socioeconomic status, etc.). The Psychometric properties and brief instrument descriptions for the PSS, CES-D, PSA, LOT-R, NSSQ, and the Brief Cope are reported in Table 1. These instruments were completed via self-administered questionnaire.

The use of medication for mental health conditions was ascertained in two ways. First, one item included in the participant questionnaire asked the following: "Do you take prescription medicines for mood or anxiety disorders (anxiety, depression, panic disorder, bipolar, obsessive-compulsive, etc.)?" Respondents could answer "yes," "no," or "stopped after I became pregnant." The question did not require the respondent to indicate which medication or to specify the disorder. Secondly, the prenatal and delivery records were reviewed for any documentation of medication use to corroborate participants' questionnaire responses, as

well as for history of depression, anxiety, panic, bipolar, or obsessive-compulsive disorder. Data collection did not include documentation of specific medication names, dosages, duration or timing of medication usage, other than for class of medication (i.e. selective serotonin-reuptake inhibitors). Depression and anxiety were analyzed as one combined variable, given that each has a high co-morbidity with the other and both were being treated with SSRIs.

Prenatal and hospital delivery records were also reviewed to obtain prenatal course and complications, medical and obstetrical history (particularly regarding previous PTB), to verify medication status, and outcome data (preterm vs. term delivery) for each participant. The records abstractor was a certified nurse-midwife researcher who was the sole data collector for the study.

Procedures

Clinic staff and providers invited each clinic attendee to speak with the researcher, who was on-site and available to inform, consent, and enroll women into the study. Informed consent was obtained by the researcher in a private exam room, using the approved consent form, and prior to any data collection. Between 14 and 20 weeks of gestation, participants had blood samples collected and received the study questionnaire to take home for completion.

A stamped and addressed envelope was provided for return of the survey within 2 weeks. Upon return of the survey, participants were given a \$10 gift card for use at local grocery/department stores. Surveys required approximately 45–60 minutes for completion.

Maternal blood samples were processed according to pre-established lab protocols.⁴⁶ Briefly, samples were immediately chilled after collection, transported to the central research lab, and processed via refrigerated centrifugation within 8 hours. Plasma aliquots were then placed into -80°C storage to await batch assay. CRH was measured using commercially prepared (Phoenix Laboratories) radioimmunoassay (RIA) kits and assay protocols, in the lab of Dr. Jeanne Ruiz at the University of Texas Medical Branch – Galveston. The RIA has an intra-assay/interassay coefficient of variability of 2-6/8.5-10%, specificity of 100% for human CRH/0% for ACTH, and a sensitivity of 0.00095–0.02 ng/ml.

The Statistical Program for the Social Sciences (SPSS) statistical software (v.17) was used for data management and analysis. Reverse coding was completed where necessary (i.e. CES-D, PSS and LOT-R instruments), data integrity was evaluated, and descriptive statistics analyzed. Square root transformation was completed for overly skewed data. CRH levels were found to have a bimodal distribution; values were clustered at opposite poles of the range of values, and included 23 women with levels below the RIA detection limits. This bimodal distribution corresponded to an approximate 75th percentile in CRH values. To rule out the possibility that the lowest and non-detectable CRH levels might be attributable to those women at the lowest gestational ages within the 14–20 week blood sample collection window, an independent samples t-test was conducted. The results indicated no difference in mean gestational age between women with CRH levels above and below the 75th percentile (17.20 weeks vs. 17.35 weeks, respectively; $t = 0.352$; $df = 98$; $p = 0.725$). Given the bimodal distribution of CRH levels, and previous documentation of associations between higher levels of CRH and PTB, the CRH variable was dichotomized at the 75th percentile for use in statistical analyses (12.5pg/mL), designated the 4th quartile as “high” CRH vs. “low” CRH for values within the lower 3 quartiles. Chi-square analyses were used to test the associations between categorical variables. Independent samples t-tests were conducted for continuous level variables. A stepwise logistic regression analysis was conducted, entering potential confounding variables (maternal age, antepartum complications, previous history of obstetrical complications, including previous PTB) into the model first. Given the

exploratory nature of the study, alpha was set at 0.1 as the entry criteria for the logistic regression analysis.

RESULTS

Out of 266 women who were scheduled for a first or “new” prenatal visit, 196 were screened for eligibility, 40 women were “no shows,” 18 women declined to be screened, and 12 women were overlooked for recruitment. Of the 196 women screened, 76 were excluded: 8 women declined to participate, and the remaining women were excluded due to exclusion/inclusion criteria; 30 non English speakers, 13 < 18 years of age, 11 at > 20 weeks gestation, 9 with non-viable pregnancies, 5 with diabetes, cardiovascular disease, or corticosteroid use. Twenty women were excluded from the study after initial enrollment; 8 who had spontaneous abortion, 3 who declined to continue participation, and 9 women who transferred to other clinics and were lost to follow-up. The final sample was composed of 100 women

Table 2 provides a demographic summary for the study sample, generally representing the demographics of the surrounding community (i.e. 69% white, 24% Hispanic, 77% married or partnered, 36% nulliparous, 33% state Medicaid recipients). Very few women reported the use of tobacco, alcohol, or social drugs (less than 5% for any one of these), which coincides with the typical surrounding community demographics and patterns.^{39, 47} One hundred women had maternal blood samples collected for CRH measurement. Eighty-five women completed questionnaires. Women who did not return questionnaires were more likely to be single ($\chi^2 = 9.19$, $p = .01$), Medicaid recipients or uninsured ($\chi^2 = 10.89$, $p = .005$), taking medications for mood and anxiety disorders ($\chi^2 = 3.42$, $p = .064$), and between 18–24 years of age ($\chi^2 = 5.34$, $p = .07$).

There were 12 participants who had a PTB. Three of these women were excluded from analysis because they were either medically induced or the birth was medically explained (1 severe pregnancy induced hypertension, 1 fetal demise at 34 weeks, 1 twin gestation). Five women had previously had a preterm birth, and three of those women again delivered preterm.

Associations were found between spontaneous PTB ($n = 9$) and the use of SSRIs for depression or anxiety prior to 20 weeks of gestation ($n = 13$ out of 100), as reported via participant questionnaire and corroborated by clinical records. An association was also found between the highest CRH levels (4th quartile, $n = 23$ out of 100) and PTB. Results of the statistical analyses (chi-square and independent t-tests) are reported in Table 3. Furthermore, a difference was found in pregnancy related anxiety scores between women delivering at term vs. preterm (10.0 vs.12.6, respectively; $p = 0.058$; $n = 85$). However, there were no associations found between PTB and most of the psychosocial stress variables.

Only those variables with significant associations with PTB were subsequently entered into the logistic regression analysis. These variables were pregnancy related anxiety, CRH, and SSRI use for depression or anxiety.

After controlling for age, antepartum complications, and any history of obstetrical complications (including previous history of PTB), the logistic regression analysis identified two independent predictors for PTB. The results of the final logistic regression model are shown in Table 4. Women who reported SSRI use for depression or anxiety at any time during the first half of pregnancy ($n = 13$, including 3 who stopped the medication upon confirmation of pregnancy) had an odds ratio of nearly 12, while women with the highest CRH levels (4th quartile) were nearly 7 times more likely to deliver preterm than those with lower CRH levels. These two predictors together accounted for 32.7% of the variance in the

outcome of PTB. No association was found between CRH levels and the use of SSRIs, nor between CRH and anxiety, stress, or depression.

While it was not a study aim to evaluate differences between women who did and did not take an SSRI for depression or anxiety, independent samples t-tests were conducted to provide this description. Table 5 provides the statistically significant results for measures of depression, perceived stress, pregnancy specific anxiety, optimism, and coping style. In spite of receiving medications for the treatment of depression and anxiety, these women scored higher on measures of depression, anxiety, and perceived stress, and lower on measure of optimism. These women also scored lower on active coping style, and higher on disengagement and self-blame coping styles.

DISCUSSION

This study did not find associations between most of the study's measures of chronic stress contributors (i.e. maternal depression, perceived stress, and low social support) and PTB. This may reflect the study's lack of power to detect these associations due to the small sample size and relative low occurrence of PTB. Nevertheless, the study did find associations between PTB, high CRH, and higher pregnancy-related anxiety scores, consistent with the few existing studies which report evaluation of these associations.^{14, 27} Furthermore, this study is consistent with reports of associations between antidepressant use (predominantly SSRIs) and PTB.^{36, 38, 48}

A thorough review of the effects of maternal mental illness on pregnancy outcomes suggests that poor pregnancy outcome, including PTB, involves complex interactions between genetic factors, health behaviors, and hormonal regulation.⁴⁸ Existing data suggest that maternal depression and/or antidepressant use during pregnancy is associated with an increased risk of PTB.^{48, 49} The pathophysiological pathway, at least for depression and PTB, may involve an increase in maternal adrenocorticotropin releasing hormone (ACTH) and cortisol levels and/or mediators of the autonomic nervous system (vasopressin and catecholamines) which drive an increased production of placentally-produced CRH.^{16, 18, 28} CRH plays a central role in the initiation of the physiological changes necessary for labor and birth.²³ This cascade of events is normal at term, but the timing occurs prematurely in the case of PTB. A proposed theoretical explanation for both chronic stress and depression/anxiety-related PTB has been forwarded by a number of researchers.^{3, 5, 12-14, 16, 17, 50, 51} However, it is unknown how the use of antidepressants may contribute to the occurrence of PTB. It is clinically plausible that those women who experience the highest and/or chronic levels of psychological distress (i.e. depression and anxiety), would be the most likely to continue medications during pregnancy. For these women, the benefits of taking medications may be perceived as outweighing any potential harm to the pregnancy. Furthermore, clinicians providing care to these women (mental health practitioners, as well as prenatal care providers) may discourage the discontinuation of medications for those women most affected by depression and anxiety, due to legitimate concern for the effects of untreated depression on the fetus and newborn, in addition to the mother.^{52, 53}

Studies provide conflicting data specifically related to depression, anxiety, medication use, and preterm birth. The reasons for these conflicts are likely due to differences in measures used, and in study populations. For example, some researchers use clinical diagnostic criteria (i.e. Diagnostic & Statistical Manual-IV-TR)⁵⁴ for diagnosing mental health disorders, while others use participant completed instruments (e.g., CES-D, Beck Depression Scale, State-Trait Anxiety Inventory etc.).

Conflicting results may also be the result of confounding variables, such as duration of depression and/or anxiety, type of medication, and amount of exposure during gestation. For example, in a large population-based study, Anderson et al 32 found no association between a diagnosis of depression or anxiety and PTB, but reported that all 18 women taking medication at discovery of the pregnancy, immediately stopped. This would indicate that women had antidepressant exposure only during the first trimester, and could certainly influence results. In many studies it is not apparent that confounding variables were taken into consideration. Small study sample size, as is the case for this study, can also render conflicting results.

It is known that stress, depression, and anxiety are highly inter-correlated. Furthermore, over 13% of women in the U.S. may be using antidepressants, predominantly SSRIs, to treat depression and anxiety during pregnancy.⁵⁵ However, it is unknown how these medications impact the physiology of pregnancy and birth, or the interaction between pregnancy physiology and mental health-related physiology. Moreover, causation cannot be assumed, and it would be clinically unwise to alter prescribing practices based on the scarce data currently available. While the results of this study indicate that CRH level and maternal use of SSRIs for depression and anxiety both predict the occurrence of PTB, no association between these two variables was demonstrated. This could indicate parallel involvement of distinctly different mechanisms for each of these predictors. A mechanism for the relationship between SSRIs and PTB has not been posited thus far by researchers.

Fortunately, the vast majority of women with depression, anxiety, chronic stress, and exposure to SSRIs do not go on to deliver preterm babies. Genetic predisposition, as well as individual allostatic load (physiologic “wear and tear” over a lifetime of stress response), could account for this.³⁰

Given that the sample size in this study was small, and that only 9 of the women spontaneously delivered preterm, we must interpret the study results with caution. Furthermore, no adjustments in statistical significance level were made to accommodate for the number of statistical tests conducted, therefore the study results could be due solely to chance. The study questionnaire was lengthy (requiring 45–60 minutes) and completed at home. This could have affected women’s ability to thoughtfully complete the questionnaire, and also provides an opportunity for the home environment to influence the responses (i.e. children, partners, interruptions). As reported, the women who did not return questionnaires (n=15) were more likely to be young, single, self-pay or Medicaid recipients, and taking medications for mood and anxiety disorders. Perhaps this reflects on the inability of a sub-sample of women (perhaps some of the more highly “stressed” and at risk of preterm birth) to complete the questionnaire.

CLINICAL IMPLICATIONS

Associations between preterm birth and maternal use of SSRIs are not currently understood. There is evidence of a higher (and perhaps equal) risk for PTB in both women with untreated depression, and those treated with an antidepressant (approximately 20%).³⁶ This might suggest that enhanced prenatal surveillance and patient education related to PTB risk, signs, and symptoms, is warranted for both groups of women.

Mental health workers, women’s health care practitioners, and prenatal care providers must work collaboratively with women who are pregnant or who desire to become pregnant, and who also suffer from depression and anxiety disorders. Caution should be used when either initiating, continuing, or discontinuing prescribed medications to treat these conditions during pregnancy. Indeed, the American College of Obstetricians and Gynecologists

recommends a multidisciplinary, individual approach to the treatment of depression during pregnancy, as well as the use of a single medication, rather than multiple medications, if antidepressant therapy is necessary.⁵⁶ A joint report by the American Psychiatric Association and the American College of Obstetricians and Gynecologists⁵⁷ provides an excellent review of potential benefits vs. harms of depression left untreated vs. pharmacotherapy and/or psychotherapy. The treatment algorithms in that joint report suggest that the treatment approach must be based on individual factors, including severity and duration of depression and/or anxiety, stability of the condition, the potential for relapse, and the threat of suicide, among other considerations.

The benefits of medication use during pregnancy must be weighed with any potential risks to the baby, as well as to the mother. A pregnant woman, along with her mental health or women's health care provider, may determine that the risk of major depression and the negative impact on her baby will surpass any potential harm of taking an antidepressant such as an SSRI. Likewise, it may be established that mild depression or anxiety disorders can be managed effectively with non-pharmacologic approaches, such as stress reduction techniques (i.e. exercise, meditation, yoga) and/or regular psychotherapy or cognitive-behavior therapy. The decision to stop, start, or continue medications during pregnancy should not be made without considering an individual woman's unique set of circumstances, diagnosis, history, and personal preferences. Informed health care providers can be a positive resource to women who are faced with making these medication decisions during pregnancy.

CONCLUSION

The results of this study suggest that women taking SSRIs for depression and/or anxiety, and those with higher levels of CRH, are at higher risk for PTB. Furthermore, these two factors appear to be independent predictors. While these results are consistent with some studies, the mechanisms are unclear, especially regarding the effects of SSRI use during pregnancy. It is important not to assume causation between SSRI use and the occurrence of preterm birth.

The Scientific Advisory Committee (SAC) on Prematurity (advisors to the National March of Dimes Campaign) has made a specific call for investigations that target the etiologic mechanisms of PTB, such as psychosocial contributors, and identification of biomarkers⁵⁸. Although numerous studies have focused on this important area, the SAC admits that the precise mechanism by which psychosocial factors influence the occurrence of PTB, as well as the potential for intervention in this area, are *largely unknown*. Midwives are perhaps well-suited, by education and philosophy, to engage in psychosocial, biobehavioral, and intervention studies in this area. Such investigations should include large sample sizes, as well as multiple measures of chronic stress and/or psychological conditions in parallel with relevant biologic measures (i.e. cortisol, CRH, immune mediators, genetic polymorphisms), and keen attention to controlling for confounding variables. This will assist researchers to better understand the mechanisms involved in psychosocial and behavioral-related PTB, and eventually to introduce and evaluate interventions having potential to reduce the risk of PTB.

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Figure One.
 Proposed Biobehavioral Pathway from Stress Response Activation to Preterm Birth

Table One**Characteristics and Psychometric Properties of Study Instruments**

Instrument	A Measure of	# of Items	Cronbach's Alpha
Perceived Stress Scale (PSS)	Perceived degree of feeling that life is unpredictable, uncontrollable, overwhelming, in a global sense in the past month	10	.91
Centers for Epidemiological Studies – Depression (CES-D)	Measures depression over the previous week	20	.93
Pregnancy Specific Anxiety (PSA)	Level of context specific anxiety, how anxious, concerned, afraid, or panicky in the past week	4	.79
Life Orientation Test – Revised (LOT-R)	Generalized expectancy of a positive outcome (optimism)	12	.79
Norbeck Social Support Questionnaire (NSSQ)	Quantity and quality of social support structures	9	
Emotional			.91
Tangible			.94
Brief COPE (14 subscales)	Coping responses to stress, such as use of distraction, acceptance, prayer, problem solving, self-blame, social support, substances, denial, etc.	28	.5–.93

Table Two

Sample Demographics (n = 100)

Characteristic	N
Ethnicity	
Hispanic	24
Non-Hispanic	76
Race	
White	69
Hispanic/Mexican	13
African/African American	4
Pacific Islander	4
Multi	4
Asian	3
American Indian/Alaskan Native	3
Marital Status	
Married	64
Living with Partner	13
Single	21
Divorced/separated	2
Parity	
Nulliparous	36
Multiparous	64
Health Insurance	
Private	56
State Medicaid	33
Uninsured/Self-Pay	11
History of Obstetric complications *	
Not applicable (never pregnant)	36
None	38
Previous PTB	5

Characteristic	N
Pregnancy Induced Hypertension	4
Previous cesarean birth	13
Gestational Diabetes	2
Placenta Previa	1
SGA	1
Oligiohydramnios	1
Fetal distress	1
Fetal demise (second trimester)	1
Recurrent spontaneous abortions	2
Postpartum depression	1
Antepartum complications in current pregnancy**	
None	40
Preterm labor	9
Bleeding/spotting	6
Pregnancy Induced Hypertension	7
Placenta previa/abruption	2
Oligiohydramnios	5
Intrauterine Growth Restriction	2
Urinary Tract Infection	4
Anemia	4
Gestational Diabetes	3
Depression	5
Stillbirth	1
Polyhydramnios	1

* Seven women experienced more than one previous OB complication

** Thirty-four women experienced more than one antepartum complication

Table Three

Results of Tests of Association with PTB

Variables	<i>p</i> value
CRH levels at 15–20 weeks gestation (n = 100 women, 23 with levels in the 4 th quartile, 7 of whom had PTB)	.001
SSRI use prior to 20 weeks (n = 13 out of 100 women, 4 of whom had PTB)	.006
CES-D (n = 85)	.917
PSS (n = 85)	.653
Functional Support (n = 85)	.430
PSA (n = 85)	.058
LOT-R (n = 85)	.903
Nutrition Score (n = 85)	.274
Sleep Quality (n = 85)	.931
Age (n = 100)	.119
Family Income (n = 85)	.487
Perception of Income Adequacy (n = 85)	.856
Education Level (n = 85)	.819
Hours worked each week for Pay (n = 85)	.758
Hours worked each week NOT for Pay (n = 85)	.246
Hours Standing per Day (n = 85)	.485
Hours lifting per Day (n = 85)	.416
Coping Style* (n = 85)	
Active	.216
Plans	.258
Reframes	.648
Accepts	.235
Uses Humor	.493
Uses Religious/Spiritual Practices	.930
Seeks Emotional Support	.337
Seeks Aid from Others	.755
Uses Distraction	.945
Uses Denial	.188
Vents	.483
Uses Substances	.587

Variables	<i>p</i> value
Disengages	.811
Blames Self	.931

CRH: corticotropin-releasing hormone

SSRI: selective serotonin reuptake inhibitor for depression or anxiety

CES-D: Center for Epidemiological Studies – Depression scale

PSS: Perceived Stress Scale

PSA: Pregnancy Specific Anxiety scale

LOT-R: Life Orientation Test- Revised scale

* Subscales from the BRIEF Cope measure of coping style

Table Four

Results of Logistic Regression Analysis for the Prediction of PTB

Variables in Model	OR (95% CI)	<i>p</i> value
CRH ^a	6.6 (1.4–31.5)	.018
SSRI use ^b	11.7 (2.2 – 60.7)	.004

CRH: corticotropins-releasing hormone (lowest 3 quartiles compared to the highest – fourth – quartile)

SSRI: selective serotonin reuptake inhibitor for depression or anxiety prior to 20 weeks of pregnancy

OR: Odds Ratio CI: confidence interval Sig.: significance level

^aThere were 23 women (out of 100) with CRH levels in the 4th quartile, 7 of those delivered preterm

^bThere were 13 women (out of 100 women) who took SSRIs prior to 20 weeks gestation, 4 of those delivered preterm

Table FiveDifferences Between Women Who Were Taking SSRIs vs. Those Who Were Not ^a

Variable	Mean (SD) Scores	<i>p</i> value
CES-D		
SSRI - YES	25.6 (14.3)	.046
SSRI - NO	17.5 (11.6)	
PSS		
SSRI - YES	24.1 (6.5)	.015
SSRI - NO	17.8 (7.7)	
PSA		
SSRI - YES	11.9 (2.5)	.074
SSRI - NO	10.1 (4.2)	
LOT-R		
SSRI - YES	13.2 (6.2)	.004
SSRI - NO	18.2 (4.9)	
Active Coping ^b		
SSRI - YES	5.0 (1.4)	.032
SSRI - NO	6.1 (1.5)	
Disengage Coping ^b		
SSRI - YES	4.6 (1.9)	.008
SSRI - NO	3.3 (1.4)	
Self Blame Coping ^b		
SSRI - YES	5.9 (1.6)	.032
SSRI - NO	4.7 (1.6)	

CES-D: Center for Epidemiological Studies – Depression scale

PSS: Perceived Stress Scale

PSA: Pregnancy Specific Anxiety scale

LOT-R: Life Orientation Test- Revised scale

^a Only statistically significant results are being reported here^b Subscales from the BRIEF Cope measure of coping style