

Prenatal Depression Risk Factors, Developmental Effects and Interventions: A Review

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Abstract

This narrative review based on a literature search in PubMed and PsycInfo on the two terms prenatal and antenatal depression includes empirical studies, reviews and meta-analyses that have been published during the last 5 years on risk factors, developmental effects and interventions for prenatal depression. Risk factor studies that met criteria feature demographic measures (lower socioeconomic status, less education, non-marital status, non-employment, less social support and health locus of control, unintended pregnancy, partner violence and history of child abuse) and physiological variables (cortisol, amylase, and pro-inflammatory cytokines and intrauterine artery resistance). The negative effects include postpartum depression, paternal depression, and prematurity and low birth weight. Negative effects on infants include greater right frontal EEG, amygdala connectivity, cortical thinning and more difficult temperament. In childhood, externalizing and internalizing problems have been reported. The data on prenatal antidepressants (specifically SSRIs) reveal negative effects including internalizing problems as well as a greater risk for autism spectrum disorder. Prenatal interventions that have been effective include interpersonal psychotherapy, peer support, massage therapy, yoga, tai chi, and aerobic exercise. Potential underlying mechanisms are discussed as well as methodological limitations including homogeneity of samples and lack of randomization to intervention groups. Despite these limitations, the literature highlights the need for prenatal depression screening and intervention.

Keywords: Prenatal depression; Risk factors; Antenatal depression

Introduction

This narrative review is based on a literature search for the terms prenatal and antenatal depression in PubMed and PsycInfo for the last five years. Exclusion criteria included non-English papers, case studies, under-powered samples and non-juried papers. Of the 213 publications found, 86 publications met criteria. These selected papers include empirical studies, reviews and meta-analyses on risk factors, developmental effects and interventions for prenatal depression. The risk factors that have been studied during this time period include demographic measures (socioeconomic status, education, marital status, employment, social support, health locus of control, unintended pregnancy, partner violence and history of child abuse) and physiological variables (cortisol, amylase and pro-inflammatory cytokines and intrauterine artery resistance).

Negative effects include poor sleep, postpartum depression, paternal depression and lower gestational age and birth weight. Negative effects on infants include lesser responsiveness of the mothers, lower Bayley scores, greater right frontal EEG and amygdala connectivity, more difficult temperament, externalizing/internalizing problems and a greater incidence of asthma. By preschool age, more behaviour problems have been noted as well as greater body mass index and less cortical thickness. At school-age greater right frontal EEG and cortical thinning are reported.

Prenatal antidepressants (specifically SSRIs) have led to negative neonatal outcomes, internalizing problems and the risk for autism spectrum disorder. Prenatal interventions that have been effective

include interpersonal psychotherapy, peer support, massage therapy, yoga, tai chi, and aerobic exercise.

Potential underlying mechanisms are discussed as well as methodological limitations including homogeneity of samples and lack of randomization to intervention groups. Despite the methodological limitations, the literature generally highlights the need for prenatal depression screening and intervention.

Prevalence and Screening

The prevalence of prenatal depression has averaged 20% in teenage pregnant women [1] and 10-25% in adult pregnant women [2]. Inasmuch as prenatal depression has been associated with all of the above problems, it has become a screening priority for the American College of Obstetricians and Gynaecologists as well as the American College of Nurse-Midwives. In one survey, 94% of nurse-midwives reported screening for prenatal depression and 72% reported the use of a standardized screening tool with 66% having used the Edinburgh Postnatal Depression Scale (EPDS) [3]. A very extensive recent literature has appeared on the psychometric properties on the use of the EPDS as a screening tool for prenatal depression, although these studies are not included in this review.

Risk Factors

In addition to the popular use of the Edinburgh Postnatal Depression Scale for general screening of prenatal depression, there are many documented risk and protective factors that might be used to formulate risk profiles as additional screening tools. Those represented

in the recent literature include demographic and physiological variables (Table 1 for risk factors).

Risk factors	Authors
Demographics	
non-working women	Fall et al. [4]
baseline depression, no partner, <exercise	Sexton et al. [5]
>Health locus of control	Moshki and Cheravi [6]
External locus of control	Richardson et al. [7]
Unintended pregnancy	Abajobir et al. [1]
Partner violence	Howard et al. [8]
History of abuse	Alvarez-Segura et al. [9]
Physiological/biochemical risk factors	
<Vitamins, >tobacco and opioids	Newport et al. [10]
Sleep disturbance, HPA dysfunction, abnormal immune function	Palagini et al. [11]
>Cortisol response to distressed infant film	Murphy et al. [12]
>Alpha amylase	Giesbrecht et al., Braithwaite et al. [13,14]
< and > pro-inflammatory function	Shelton et al. [15]

Table 1: Prenatal depression risk factors.

Demographics

These have included socioeconomic status, marital status, employment, education, physical activity, social support, health locus of control, unintended pregnancy, partner violence and history of child abuse. In a multivariate logistic regression model, several variables were explored including employment, education, social support, socioeconomic status, marital status and smoking [4]. In this study, the Center for Epidemiological Studies Depression (CES-D) scale was used to identify prenatal depression in 5,337 pregnant women at 24-26 weeks gestation. The prevalence of depression in this population was 12%. Working women had a significantly lower rate of depression symptoms (8%) than housewives (19%), women who had stopped working (14%) and students (14%). In multivariate analyses, the factors that were significantly associated with prenatal depression were low education, low social support outside of work, acute stressful events, low income, marital strain, a chronic health problem, country of birth and smoking. Surprisingly, although rates of prenatal depression were compared for working and non-working women, work status was not a significant risk factor in the multivariate analyses.

Health and external locus of control are also risk factors, although they have accounted for very little of the variance in prenatal depression scores. In a study on health locus of control, prenatal depression based on the EPDS was experienced by 37% of the sample of 208 Iranian pregnant women [6]. Social support and health locus of control were significant predictors of depressive mood in a linear regression model. In a study on American pregnant women (N=133 rural women), external locus of control scores accounted for 17% of the variance in EPDS scores [7]. The small per cent of the variance

accounted for in these studies highlights the importance of multivariable studies especially for the development of risk profiles.

Other risk factors for prenatal depression include unintended pregnancy, partner violence and a history of child abuse. In a meta-analysis on unintended pregnancy, the prevalence of prenatal depression was 21% or twofold in women who had an unintended pregnancy [8]. Another meta-analysis on 67 papers focused on partner violence during pregnancy [9]. A three - fold increase in depression was noted in those who had experienced partner violence during pregnancy. In a systematic review of 545 studies, 43 met inclusion criteria on the association between history of abuse and prenatal depressive symptoms [10]. The high number of papers screened for this review (545) is probably not surprising since they searched five databases from the start dates of the search engines through 2011. But very few studies (less than 10%) met inclusion criteria, highlighting the variability of the studies on recruitment methods, prenatal depression measures and/or outcome measures.

In a study on predictors of recovery from prenatal depression based on the Beck Depression Inventory (BDI), women who recovered (only 39%) had lower depression scores, cohabited with a romantic partner and exercised more frequently [5]. These two studies are exemplary for their exploration of multiple variables, although the variance explained by these factors is very low.

This literature on demographic risk factors seems limited by its primary focus on single variables such as partner violence and a history of child abuse that individually contribute very little to the variance on prenatal depression. And, in the very few multivariate studies, several risk factors were statistically significant but, again, did not account for very much of the variance in prenatal depression. Screening could include not only depression scales but also demographic and physiological variables that have been documented as significant predictors. Profile analysis could be conducted to determine risk profiles.

Physiological risk factors

A broad array of physiological variables has appeared in the recent literature on prenatal depression including vitamins, tobacco, cortisol, alpha amylase, dopamine and pro-inflammatory cytokines. In a study on 195 pregnant women, prenatal vitamin exposure was negatively correlated with depression while tobacco and hypnotic exposure, antiemetics and opioid analgesics were positively correlated with prenatal depression [10]. Although statistically significant, most of the correlations in this study were low and likely not clinically significant.

In a systematic review on longitudinal studies using four databases, 20 studies met inclusion criteria for the relationship between prenatal depression and sleep loss, hypothalamic - pituitary - adrenal (HPA) function and abnormal immune/inflammatory reactions [11]. These variables, in turn, were related to negative pregnancy outcomes. This review is exemplary for its multivariate focus and inclusion of several self-report as well as hormone and immune function variables and could be a model for reviews on the prenatal depression risk factor literature.

Although the HPA system has been implicated as a potential underlying biological mechanism for the relationship between prenatal depression and adverse neonatal outcomes, very little is known about whether HPA reactivity is enhanced in prenatally depressed women. In a recent study, prenatally depressed women (between 11 and 18 weeks gestation) were exposed to a distressed infant film and their salivary

cortisol and mood responses were assessed [13]. Cortisol increased which supports altered HPA axis functioning as a potential underlying mechanism for prenatal depression effects on fetal development. Because the findings have been mixed on the relationship between elevated cortisol and adverse neonatal outcomes, others have been exploring depression effects on alpha-amylase.

Like cortisol, alpha-amylase is considered a depression - related stress hormone representing sympathetic activation. In a recent study, diurnal patterns of salivary alpha-amylase and mood were studied in 83 pregnant women [16]. Depressed mood was associated with increased alpha-amylase. Because it can be assayed in saliva samples, it is also a low cost measure. In another alpha-amylase study by a different research group, depressive symptoms on the EPDS were assessed along with diurnal salivary alpha-amylase levels [15]. In this study on 76 pregnant women, those with depression symptoms during the third trimester had elevated alpha amylase levels upon awakening and the elevated levels continued throughout the day across the course of two days. The authors concluded that increased vasoconstriction and reduced blood flow to the fetus could mediate the association between prenatal depression and adverse neonatal outcomes.

Prenatal depression and cortisol have also been related to decrease pro-inflammatory and anti-inflammatory cytokines. In a study on 105 pregnant women, blood samples were collected between 16 and 20 weeks gestation to explore these relationships [16]. Depressive symptoms were inversely correlated with three cytokines including interleukin (IL)-1beta, tumour necrosis factor (TNF) and IL-7. In the same study cortisol was inversely related to the same pro-inflammatory cytokines (IL-1beta and TNF) as well as anti-inflammatory cytokines (IL-4, IL-5, IL-10 and IL-13). These data suggest that both excessive and inadequate inflammation is related to prenatal depression symptoms.

This latter study [16] is an example of research that is needed to form demographic/physiological profiles for screening pregnant

women at risk for prenatal depression. The multi-variable nature of the study including not only a self-report of depressive symptoms, but also measures of the stress hormone cortisol and pro and anti-inflammatory cytokines would enable the design of a more accurate profile to be used in screening pregnant women at risk for prenatal depression. Alpha-amylase could be added to the relatively inexpensive saliva cortisol assays as could the demographic variables identified as risk factors in this recent literature search. Those, In turn, could be added to the screening process that could take place during the first prenatal visits. Women could then be referred to stress reducing activities and therapies to prevent the undesirable obstetric complications, neonatal outcomes and developmental problems associated with prenatal depression.

Developmental Effects of Prenatal Depression

Although many developmental problems have been identified in earlier literature reviews on prenatal depression effects, only those found during the last 5 years are discussed here (table 2 for developmental effects). Those include poor sleep and postpartum depression for the mother; paternal depression for the father; and non-optimal neonatal outcomes including lower gestational age, birth weight, Apgar and Brazelton scores as well as less exclusive breastfeeding. Developmental problems for infancy include sleep problems, less maternal responsivity, less optimal performance on the Bayley Developmental scales, greater right frontal EEG activation, greater connectivity to the amygdala, difficult temperament, externalizing and internalizing behaviours and asthma. By the preschool stage the children of prenatally depressed women have less frontal cortical thickness, greater behaviour problems and a higher body mass index. During childhood they experience greater right frontal EEG activation, greater cortical thinning of the frontal lobes and a twofold increase in mental disorders.

Effects	Measures	Authors
Pregnant women		
Sleep problems	Pittsburgh Sleep Quality Index	Tham et al. [16]
Sleep problems	Pittsburgh Sleep Quality Index	Tham et al. [16]
Postpartum depression	EPDS scores	Milgrom et al., Choi et al. [17,18]
Paternal depression	EPDS scores	Konishi et al. [19]
Neonatal outcomes		
Preterm birth		Liu et al. [20]
Low birth weight		
Preterm birth, low birth weight and <Apgar scores		Nylen et al. [21]
<Breastfeeding	Initiation and exclusive	Figueiredo et al., Grigoriadis et al. [22,23]
<Optimal neonatal behaviour	Brazelton scores	Gerardin et al. [24]
Infancy		
>Cortisol responses @ 2 mos.	Immunizations	Fernandes et al. [25]

<Self-regulation	Heel stick	Warnoch et al. [26]
<M responsiveness to 12 mo. infants	Observations	Pearson et al. [27]
<M response to I faces	Laboratory paradigm	Macrae et al. [28]
<M interpretation of I faces	Laboratory paradigm	Webb and Ayers [29]
>I temperament	Self-report	Lee and Hans [30]
>right frontal EEG activation @ 6 mos. Laboratory		Kerstis et al. [31]
>Connectivity amygdala @ 6 mos.	fMRIs	Soe et al. [32]
>Externalizing/internalizing @ 24 mos.	Self-report	Soe et al. [32]
Behaviour problems toddlerhood	Interviews	Edwards and Hans [33]
Emotional/behaviour problems preschool	Self-report	Tao et al. [34]
Behaviour problems grade and high school	Self-report	O'Donnell et al. [35]
Internalizing problems @ 14 years	Youth self-report	Betts et al. [36,37]
Externalizing problems @17 years		
Depression @ 18 years		Quarini et al. [38]
Depression @21 years		Betts et al. [37]
>Right frontal EEG activation @ school age	Happy and sad film clips	Feng et al. [39]
<Cortical thickness 2-5 years	fMRIs	Lebel et al. [40]
>Cortical thinning 6-9 years	fMRIs	Sandman et al. [41]
>Body mass index @ 3 years		Cheng et al. [42]
>Asthma @ school age		Ross et al. [43]
Antidepressant effects		
<gestational age and Apgar scores		Ross et al. [43]
>Internalizing @ 3 years		Oberlander et al. [44]
Autism spectrum disorder @ 6 years		Boukhris et al. [45]
>Interaction behaviours		
<Behaviour problems @ preschool and 7 years		Pedersen et al. [46]
<Overweight in girls @ preschool and 7years		

Table 2: Developmental effects of prenatal depression.

Problems for the Pregnant Women

The negative effects of prenatal depression on pregnant women include sleep disturbances and continuing depression into the postpartum period. In one study, sleep quality during pregnancy was not only associated with prenatal depression symptoms but also with postnatal depression [16]. Unfortunately, as in many other studies, this research relied on self-report measures including depression scores on the EPDS and sleep ratings on the Pittsburgh Sleep Quality Index. In a much larger sample study from Australia, 3,144 women of a total sample of 35,374 women had a score greater than 12 on the EPDS [17]. Prenatal depression along with a history of depression and low partner support were the strongest predictors of postpartum depression. Again this study was totally reliant on self-report measures, as would be

expected with a sample that large. In a smaller sample (N=467) from Korea, 26% had EPDS scores >10 and prenatal and postpartum depression scores were significantly correlated ($r=0.60$) [18]. Surprisingly, no data on pre-pregnancy depression are included in these studies. Prenatal depression that continues as postpartum depression may relate to a hormonal imbalance, an unwanted pregnancy or equally as likely a manifestation of chronic depression.

Paternal depression

The prevalence of prenatal paternal depression is noted to approximate that of prenatal maternal depression. In a Japanese sample, self-reported depression by the men was greater than that reported by their female partners (10% vs. 2%) [19]. These very low

incidence figures are not surprising given that, according to the authors, Japanese couples tend to suppress their real emotions to avoid confrontation.

Neonatal outcomes

In a very large sample study on 366,499 singleton births in Sweden, paternal prenatal depression was associated with very preterm birth (22-31 weeks gestation) and maternal prenatal depression was associated with an increased risk of moderately preterm birth (32-36 weeks gestation) [20]. One possible explanation for the more severe prematurity association with paternal prenatal depression is that paternal depression is often comorbid with maternal depression [19]. The depression of both parents would likely contribute to the shorter gestation and the mother's depression would likely be exacerbated by the father's depression. On a sample that size, those questions could be explored.

In a systematic review and meta-analysis based on PubMed and PsychInfo databases, 50 published reports were found on preterm birth and 33 on low birth weight [2]. Based on their meta-analysis, less than half the 50 reports on gestational age noted a significant association between prenatal depression and preterm birth while slightly more than half of the 33 reports on low birth weight revealed a relationship to prenatal depression. This suggests that the effects of prenatal depression on low birth weight are more consistent than those on preterm birth. In contrast, in a study on 691 women in Korea, prenatally depressed women were more likely to deliver preterm and low birth weight infants, but the association for prenatal depression and low birth weight was attenuated when the analysis was adjusted for gestational age [47]. In a study from the US on 235 pregnant women, the new-borns of depressed women were born earlier, weighed less and had lower Apgar scores than the new-borns of non-depressed women [21]. This was particularly true for pregnant women who claimed to have less support from their partners.

Preterm delivery and low birth weight are two of the most frequently reported adverse neonatal outcomes following prenatal depression. But it is not clear that a disproportionate number of preterm births are to prenatally depressed women, and it is not clear from these studies what depression-related variables may be mediating these effects. For example, having less support from partners was a contributing variable in the study just summarized [21]. And, several biochemical variables have been mediators in previous studies. For example, cortisol has been a mediator of preterm delivery and norepinephrine a mediator of low birth weight in earlier studies [48]. Intrauterine artery resistance is also a likely mediator as it results in limited flow of nutrients and oxygen to the fetus and has been associated with elevated norepinephrine, although no studies were found on this variable as a mediator in this review of the literature.

Initiations of breastfeeding and exclusive breast-feeding have also been affected by prenatal depression. In one study on 145 women who completed the EPDS during the second and third trimester as well as across the first year, the EPDS scores during the third trimester were the best predictors of exclusive breastfeeding duration (a negative relationship) [22]. In this study, a significant decrease in depression scores was noted from childbirth to three months postpartum in those women who engaged in exclusive breastfeeding. It is not clear whether the exclusive breast-feeding was enabled by decreased depression or whether the breastfeeding contributed to the decrease in postpartum depression or both. In a systematic review and meta-analysis on the impact of prenatal depression on neonatal outcomes and breast-

feeding, only 30 studies met criteria of the 3,074 abstracts reviewed (less than 1%) [23]. In these studies, preterm delivery and breastfeeding initiation were significantly associated with prenatal depression.

Unfortunately none of the studies on developmental effects of prenatal depression included biochemical variables. For example, it is possible that elevated cortisol levels in these prenatally depressed women led to lower oxytocin levels which, in turn, would affect the ability to breastfeed. The degree to which the depressed mood and vegetative symptoms and/or the hormonal imbalance affected the initiation and then the duration of breastfeeding is unclear and needs to be examined. Intranasal oxytocin might be a simple therapy to facilitate breastfeeding. And, breastfeeding itself would then increase oxytocin levels that might contribute to the duration of exclusive breastfeeding. Being the "love hormone" it might also contribute to the "bonding" relationship between the infant and parents. It is surprising in this light that the relationships between prenatal depression, oxytocin levels and breastfeeding have not been explored in recent research especially since oxytocin levels assayed from saliva samples are reputedly reliable.

Neonatal behaviour has also been affected by prenatal depression [24]. In this study on 205 pregnant women who met the DSM - IV criteria for a major depressive episode, the male new-borns of prenatally depressed women had lower scores on the motor maturity and state regulation clusters of the Brazelton Neonatal Behaviour Assessment Scale. At a one-year follow-up, based on the Infant-Toddler Social and Emotional Assessment scores, infants of prenatally depressed versus non-depressed mothers had higher depression and anxiety scores, particularly the male infants, who also had impulsivity and sleep problems. These neonatal data would appear to be robust as they are based on assessments by "blind" assessors on the relatively objective, psychometrically sound Brazelton scale and they are consistent with previously reported data [2]. However, the one-year follow-up data on infant depression, anxiety and impulsivity are unique to this study and need to be replicated.

Infancy

In contrast to the prenatal depression/neonatal outcome literature, very little research has been published recently on the effects of prenatal depression on infants. In one study, prenatal depression predicted elevated cortisol responses of two-month-old infants to immunizations [24]. This study, surprisingly, showed that the mothers with the highest as well as those with the lowest EPDS scores had infants with the most elevated cortisol responses. The authors suggested that moderate amounts of fetal stress may lead to a greater ability to regulate responses to stressful stimuli in infancy. An alternative possibility is that the mothers with the lowest scores may have been "faking good" (under-reporting or denying their depression), a phenomenon that has been noted in at least one other study [49].

Most of the recent papers on prenatal depression effects on infants have focused on mothers' responses to infant expressions and behaviours during early interactions as well as infant difficult temperament and infant brain patterns. An example is the responses of mothers with prenatal depression and/or anxiety during an infant heel lance procedure [26]. The mothers who had been prenatally depressed spent significantly less time embracing and engaging with their infants or responding to infant cues during the heel stick procedure. The mothers' behaviour was, in turn, related to atypical self-regulation by

the infant in response to pain both during and after the heel stick. In another study from the UK, in a sample of 900 women, those with high depression scores during mid-pregnancy had a 30% increased risk of low maternal responsiveness towards their 12-month-old infants [28]. Surprisingly, the mothers' depression scores at eight months were not related to their lack of responsivity at 12 months.

Maternal-like responsivity has also been assessed in a laboratory situation where women have been presented with photos of distressed, neutral and happy infant faces [28]. In this study, prenatally depressed and non-depressed women rated their responses to these faces on three dimensions including wanting to comfort, wanting to turn away and feelings of anxiety. The women who were prenatally depressed were less likely to want to comfort the distressed infant and more likely to want to turn away from the distressed infant. In a similar paradigm, prenatally depressed and non-depressed women were assessed at 11 weeks gestation on their ability to disengage attention from infant and adult faces showing positive, negative and neutral emotions [27]. The depressed women took less time to disengage attention on the distressed infant faces versus the non-distressed faces.

In a systematic review of 14 studies on prenatal depression effects on interpretation of infant emotional expressions, the depressed pregnant women were less accurate at identifying happy faces in the infants and more likely to identify sad faces [29]. The prenatally depressed women also disengaged faster from both the happy and the sad faces of the infants.

These data are not surprising inasmuch as depressed individuals are noted to experience more withdrawal emotions accompanied by relative right frontal EEG activation with the right frontal region noted for processing negative emotions. The depressed individuals may be processing emotions, especially negative emotions, more rapidly and withdrawing from them because of the greater activation of the right frontal region of the brain. This is another example of how a multivariate approach would help clarify the process. For example, the withdrawal from distressed infant faces may have been accompanied by right frontal EEG activation.

Perceptions of infant temperament have also been assessed in prenatally depressed women. In one study, 248 low incomes, African-American women between 13 and 21 years of age reported on their depression symptoms and their child's temperament at the third trimester pregnancy and across infancy [30]. Approximately one-half of the young mothers who scored above the clinical cut-off for prenatal depression perceived more child and parent-child interaction difficulty than the non-depressed across the first two years of development. The continuing perception of difficult interactions across infancy may have related to chronic depression in the mothers and/or to actual difficult interactions that have been documented in several studies [2].

Both prenatally depressed mothers and fathers view their infants as having difficult temperaments. In a study on 401 Swedish-speaking couples, both the mothers (18% being depressed) and fathers (9% being depressed) perceived their child's temperament as being more difficult as compared to the perceptions of non-depressed parents [31]. Again, this may have not only been perceptions but accurate observations as infants/children of prenatally depressed parents have been noted to have difficult temperaments. Unfortunately these perceptions were not validated by observations, which could have been conducted on a subsample of the Swedish study.

Negative perceptions of infant temperament may also relate to depressed parents' expectations that their offspring may develop

depressive behaviours similar to their own. They may expect a familial transmission of their own mood disorders. An example of this possibility comes from a study on increasing maternal depression symptoms from the prenatal to postnatal period predicting greater relative right frontal EEG activation, a marker of depression, in six-month-old infants. In addition, prenatal and early postnatal depression symptoms in the mothers predicted infants' externalizing and internalizing behaviours by the end of infancy. The authors suggested that these findings "may reflect a neural basis for the familial transmission of phenotypes associated with mood disorders, most particularly in girls". A similar study that was focused on "potential transgenerational transmission of vulnerability for affective disorders" assessed depression at 26 weeks gestation and three months after delivery using the EPDS and infants' fMRI's at six months of age. Infants born to mothers with higher prenatal depression scores showed greater functional connectivity of the amygdala with the anterior cingulate and the prefrontal cortices. The authors claimed that these data were consistent with connectivity patterns that have been reported for adolescents and adults with major depressive disorder. This phenomenon has been referred to as fetal programming, a model that has been advanced for understanding the persistent effects of prenatal depression on child development.

Continuity of Problems from Infancy across Development

Several research groups have reported the continuity of problems from infancy across development. Among those developmental problems that appear to emerge during infancy and continue through toddlerhood, preschool, school-age and adolescence are the behaviour problems and brain patterns just discussed as well as some physical conditions including greater body mass index and asthma. As in the study showing emerging externalizing and internalizing behaviours by the end of infancy, others have shown similar problems. For example, in a sample of 196 interviews of young, low income African American mothers, path analyses revealed a relationship between prenatal depression and toddler behaviour problems that was mediated by maternal sensitivity, with boys being especially susceptible to maternal sensitivity. In a large sample study on the relationship between prenatal depression and emotional and behavioural problems in preschool children (N=3,653) in China, 6% of the pre-schoolers showed emotional problems, 8% conduct problems, 8% hyperactivity and 3% peer problems. These rates seemed high relative to their low rate of prenatal depression during the first trimester (5%) and in the second trimester (4%). Fortunately, in the logistics regression on this data set, several potential confounds were controlled including gestational age, family income and parental education.

In the Avon Longitudinal Study of Parents and Children (N=7944) in England, more behavioural and emotional symptoms were noted across childhood and into adolescence in the offspring of women who had high levels of prenatal depression or anxiety [35]. The authors concluded that their data support the fetal programming hypothesis. In still another large data sample from Australia (N=3,925 mothers), multivariate logistic regression models on prenatal depression, anxiety and stress were conducted to predict internalizing and externalizing behaviours at age 14. After adjusting for potentially confounding variables, prenatal symptoms uniquely predicted internalizing, but not externalizing problems. In contrast, the results of a study from Finland suggested that prenatal depression (based on the EPDS) was associated with externalizing problems on the Youth Self Report (YSR). Although

this was a normal population sample with a relatively small number of prenatally depressed women, exclusive self-report data and a high drop-out rate, the long-term effects at 17 years highlight the need for prenatal screening and intervention.

Still longer-term effects have been noted in follow up samples of the Avon longitudinal study and the Australian study. In the Avon longitudinal study, the follow-up sample at age 18 (N=7959) was assessed for depression. The odds ratio for offspring depression at age 18 was significantly higher for girls than boys. Still later at age 21, increased behaviour problems and depressive symptoms were noted in the offspring of the prenatally depressed Australian women. Although this research group has continually adjusted for a number of potential confounding variables including maternal life events, concurrent maternal depression, paternal depression and relationship quality, the maternal trajectories used in their multivariate logistic regression models included not only prenatal depressive symptoms but also anxiety and stress symptoms, thus confounding the specific effects of prenatal depression. Finding a purely depressed sample is difficult given the frequent comorbidity of prenatal depression and anxiety.

A continuity of brain patterns is suggested by the similar findings on right frontal EEG activation (asymmetry) in 6 month old infants already summarized and in school-age children. In the school-age study, 43 children born to mothers with childhood onset depression were assessed on the Children's Depression Inventory and their EEG was recorded at baseline and during their observations of happy and sad film clips. Children with elevated depression symptoms showed relative right frontal EEG asymmetry both at baseline and while watching the film clips. As the authors suggested, this consistent right frontal EEG asymmetry may be a marker of child depression, as it has been in adults.

In a magnetic resonance imaging study, 52 women who had completed the EPDS during each trimester of pregnancy were recruited for the study and their children underwent magnetic resonance imaging when they were 2 to 5 years of age to measure cortical thickness. The women's second trimester EPDS scores were negatively correlated with their children's cortical thickness in both the right inferior frontal and medial temporal regions. In a similar study but on children 6 to 9 years of age, 81 children received a magnetic resonance imaging scan. In this study prenatal maternal depression was associated with cortical thinning in their children, primarily in the right frontal lobes. Exposure to maternal depression at 25 weeks gestation was associated with cortical thinning in 24% of the frontal lobes and in 19% of the whole cortex. In addition, the significant correlation between prenatal depression and the children's externalizing behaviour was mediated by cortical thinning in the prefrontal areas of the right hemisphere. The data from these studies combined highlight the vulnerability of brain development in the offspring of prenatally depressed women.

Other developmental continuity problems that have been associated with prenatal depression include body mass index and asthma. In a mixed (N=284) sample of adolescent and adult mothers with low and high education, prenatal depression symptoms were assessed by self-report and parenting behaviour was assessed by both self-report and observational methods at 4,6 and 8 months. The children's self-regulation behaviour was then assessed at 24 and 30 months and the children's body mass index at 36 months. Structural equations analysis suggested that prenatal depression symptoms predicted less positive parenting which, in turn, predicted lower levels of child regulation which, in turn, predicted higher body mass index at three years of age.

Similar patterns of prediction were noted across the different age and education group mothers. This comprehensive study on a relatively representative sample highlights the complex interactions between prenatal depression, later parenting, child behaviour and physical problems such as early onset obesity.

The continuity of asthma as a developmental condition related to prenatal depression is shown in a study on infants with asthma and a review of studies on children with asthma. In the infant asthma study, 1,152 women were assessed for prenatal depression at 26 weeks gestation on the EPDS and the mothers later reported on their infants' asthma and eczema symptoms. Increased asthma symptoms were noted in infants of women with PDS scores greater than 15. Given that asthma and eczema are often comorbid, it is surprising that prenatal depression was not related to infantile eczema. In a systematic review and meta-analysis, four electronic databases were searched for a relationship between prenatal depression/stress and asthma. The 10 studies in the meta-analysis suggested a greater prevalence of wheezing and asthma in children exposed to prenatal depression/stress.

In a systematic review, a broader array of short and long-term effects was noted for the offspring of prenatally depressed women. This review on 43 articles documented effects on the fetus including hyperactivity and an irregular fetal heart rate. Negative effects on the new-born included increased cortisol and norepinephrine, decreased dopamine, greater right frontal EEG activation, lower vagal activity, depressive-like behaviours and increased rates of premature deaths and admission to the neonatal intensive care unit. In children, increased cortisol levels, internalizing and externalizing problems and overweight effects were reported. And, in adolescents, a relationship was noted between prenatal depression and a "slight increase in criminal behaviour". The author highlighted untreated prenatal depression as being a risk factor for all of these developmental conditions and the need for comparisons between untreated prenatal depression and prenatal exposure to antidepressants.

Prenatal Depression Interventions

Prenatal interventions have included antidepressants and complementary therapies. Because of the mixed data on antidepressants, recent prenatal intervention research has focused on complementary therapies (Table 3). These have included interpersonal psychotherapy and peer support groups as well as physical therapies including massage, yoga, tai chi and exercise.

Interventions	Authors
Interpersonal psychotherapy	Spinelli et al. [50]
Interpersonal psychotherapy vs. peer support	Field et al. [51]
Yoga vs. massage therapy	Field et al. [52]
Yoga vs. social support	Field et al. [53]
Tai chi/yoga	
Yoga	Gong et al. [54]
Exercise	Robledo-Colonia et al. [55]
	Perales et al. [56]

Table 3: Prenatal depression complementary therapies.

Antidepressants

For those depressed pregnant women who were exposed to antidepressants (most particularly SSRIs) some experienced non-optimal outcomes. However, the literature on selective serotonin reuptake inhibitors (SSRIs) for prenatal depression is mixed, with other studies showing better outcomes.

In a study that combined data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, providers reported antidepressant use 25% of the time for all visits by depressed pregnant women [57,58]. Non-Hispanic white women were more likely to use antidepressants than Hispanic white women.

Studies from the last five years have yielded inconsistent effects from prenatal antidepressant use, with different effects being noted for different variables at different stages. First for the negative effects of prenatal antidepressants, non-optimal birth outcomes have been noted, as well as greater internalizing behaviours, and a greater risk for autism spectrum disorder. In a systematic review and meta-analysis of 735 articles of which only 23 met criteria, preterm delivery and lower Apgar scores were associated with prenatal antidepressant exposure. In a study comparing 33 serotonin reuptake inhibitor exposed children with 42 non-exposed children at age 3 years, prenatal exposure was associated with increased internalizing behaviours. In a Canadian study on 145,456 full-term infants, antidepressant use (selective serotonin reuptake inhibitors) during the second and/or third trimester was associated with an increased risk of autism spectrum disorder by six years of age [59].

Prenatal exposure to serotonin reuptake inhibitors (SRIs) has also had positive effects including infants showing better early interaction behaviours, having less behavioural and emotional problems as preschoolers and less overweight in females at preschool age. In a study on 32 depressed mothers with prenatal SRI treatment as compared to 42 without treatment, the SRI exposed infants (Mage=3 months) showed more readiness to interact during a toy session, even though their mothers interrupted their infants during toy play despite their being on antidepressants. The effects of prenatal antidepressants are confounded in this study by the continuing use of antidepressants at 3 months post-delivery.

In the Danish National Birth Cohort study, untreated prenatal depression was associated with abnormal Strengths and Difficulties Questionnaire scores (behaviour problems) at preschool age while prenatal antidepressant exposure was not associated with abnormal scores. In a study from Australia, 71 received prenatal SSRIs, while 204 did not and 6285 were not prenatally depressed [60-63]. At preschool age, females of exposed mothers were less likely to be overweight when compared with females whose mothers were not treated. This finding was not observed in the male offspring. However, in a follow-up study by the same group, 7 year old males who had been exposed were at increased risk for being overweight while the SSRI exposed females were still less likely to be overweight. And, the 7 year old children had fewer behaviour problems as well.

Both the positive and negative effects data on the use of prenatal SSRIs are tenuous at best as these were not randomized controlled studies and the groups being compared (the SSRI treated and untreated) may be self-selected groups that differ on a number of potentially confounding baseline variables. Although many of the researchers suggested that they had controlled for level of prenatal depression, many other demographic and pregnancy variables could

have been unknown and not controlled in their data analyses. Now that the literature on prenatal SSRIs is known to be mixed, it is unlikely that randomized controlled trials would be ethically allowed for comparing SSRI treated and untreated women and their offspring. These mixed findings highlight the need for alternative therapies that would not have negative effects.

Complementary Interventions

At least ten studies were found on alternative interventions for prenatal depression during the past five years. They include interpersonal psychotherapy, peer support groups, massage therapy, yoga, tai chi/yoga, and aerobic exercise. In a randomized, single-blind, controlled clinical trial, interpersonal psychotherapy was compared to a parenting education program. For this data analysis, 75 participants who met DSM-IV criteria for major depressive disorder and scored greater than 16 on the Hamilton Depression Rating Scale were randomly assigned to the two groups. Although there were no significant treatment group by visit interaction effects, post hoc analyses suggested illness improvement and lower illness severity on the Clinical Global Impressions Improvement scale for the interpersonal psychotherapy group, with the scores for the parenting education program group remaining relatively unchanged.

In another comparison of an interpersonal psychotherapy group but this time with a peer support group, 20 min sessions were held once per week for four weeks for the peer support group and one hour long sessions for the interpersonal psychotherapy group. Prenatal depression was assessed by the Center for Epidemiological Studies-Depression (CES-D) scale and anxiety and anger were measured by the Spielberger state anxiety and state anger scales in this study [64,65]. Even though the peer support group had lower socioeconomic status and higher depression scores at the beginning of treatment as well as having shorter group sessions, the groups were equivalent on depression scores at the end of the treatment period. Saliva cortisol levels also decreased for both groups, although the decrease was greater for the peer support group. The groups were also equivalent on neonatal outcomes including gestational age and birth weight. Although the data showing better effects for the peer support group need to be replicated, the data do suggest that peer support groups can be effective and certainly cost-effective.

In a study comparing the effects of yoga and massage therapy 84 prenatally depressed women were randomized to yoga, massage therapy or a standard care control group. Twice weekly 20 min sessions were held for 12 weeks. At the end of the 12 week period, both therapy groups had a greater decrease on depression, anxiety and pain scales and improved relationships with their significant other. The yoga and massage therapy groups also had better neonatal outcomes including greater gestational age and birth weight than the control group. The similar outcomes for the massage therapy and yoga groups suggest that they may have a common underlying mechanism, e.g. the stimulation of pressure receptors leading to greater vagal activity, lower cortisol and ultimately greater gestational age and birth weight.

In another study the effects of yoga (physical poses) and peer support group (verbal interaction) were compared on pregnancy and postpartum measures [66,67]. At the end of the first and last sessions the yoga group as compared to the peer support group reported less depression, anxiety, anger and leg and back pain. However, following 12 weeks of 20 min sessions held once per week, both groups had lower depression, anxiety and anger scores which persisted at the postpartum

follow-up assessment. Saliva cortisol levels also decreased for both groups following each session as well as estradiol and progesterone levels. To add more movement to these exercise sessions, the standing yoga poses were combined with tai chi movements in another study. The tai chi/yoga group participated in 20 min group sessions once per week for 12 weeks and was compared to a waitlist control group. As compared to that group, the tai chi/yoga group had lower depression (CES-D) scores as well as lower negative affect and somatic/vegetative symptoms (CES-D) subscale scores, lower anxiety scores and lower sleep disturbance scores.

In a systematic review and meta-analysis of six randomized controlled trials (RCTs) on yoga for prenatal depression, 375 pregnant women were diagnosed using the Structured Clinical Interview for DSM-IV and the CES-D scale. In these RCTs, yoga groups were compared to standard prenatal care, prenatal exercise and social support groups. The overall comparison suggested lower levels of depression in the yoga groups including both the prenatally depressed women and non-depressed groups. The exercise group may have had lower compliance and higher attrition rates given the greater exertion required.

More traditional forms of exercise have been tried with prenatally depressed women. In one study an exercise group was compared to a control group who continued their usual activities. This was a randomized trial that included blinded assessors and intention-to-treat analyses. Eighty pregnant women were randomly assigned to a three month supervised exercise program that started in the second trimester with each session including 10 min of walking, 30 min of aerobic exercise, 10 min of stretching and 10 min of relaxation. At the end of the 12 week intervention, the exercise group had lower scores on the depression (CES-D) scale. A larger sample would be needed to assess the differential effects of these various forms of exercise. In a similar study, 184 women were randomly assigned to an exercise group or a control group, with the exercise group attending three one-hour sessions per week throughout. By the end of the study, the exercise group had significantly lower CES-D scores and a lower percentage of the exercise group was depressed (12 versus 25%) [68-70].

In a systematic review including Medline and PubMed searches, 49 papers were found on barriers and facilitators of prenatal depression intervention and 17 papers on interventions in obstetric settings. The barriers to providing prenatal intervention included stigma, limited obstetric provider training and resources and limited access to mental health treatment. The facilitators included screening and referral processes, health care providers empowering women, obstetric provider and staff training and improved mental health resources [71-75]. Apparently the same factors, for example, obstetric provider and staff training, have been barriers in some places and facilitators in other places.

A continuing problem with the prenatal depression intervention research is the lack of randomized controlled trials. As interventions are shown to be effective, it will be increasingly difficult to ethically conduct randomized controlled trials involving standard treatment control groups, as in depriving the control group of a notably effective therapy [76-78]. However, randomization to treatment comparison groups to assess the relative efficacy of the therapies including their cost-effectiveness would help inform the process. Having established the importance of screening and referral, the need now is for not only more accurate screening but also for intervention protocols that can be used by obstetric providers.

Limitations of this Recent Literature

The research on prenatal depression from the last 5 years has featured new measures, conditions and types of studies. The new measures have included fMRIs, alpha-amylase as a complementary stress hormone to cortisol, and cytokines as an index of pro-inflammation and anti-inflammation [79]. New developmental conditions have included overweight, autism spectrum disorder and cortical thinning, suggestive of more severe prenatal depression effects. New types of studies including systematic reviews and meta-analyses have been enabled by the accumulating empirical studies on prenatal depression. These, however, have been limited to less than 10% of relevant papers and even as few as 1% of the papers meeting inclusion criteria. This limited number likely derives from variable screening methods and outcome variables that make the studies difficult to compare in meta-analyses and simple statistical problems like missing standard deviations. Researchers may need to study meta-analysis inclusion criteria to ensure that their studies can be included in meta-analyses. However, some of the inclusion criteria such as randomization may not be feasible because of the inherent difficulty of random assignment for this research including the ethical problems of assignment to anti-depressant vs. untreated groups and to therapy versus non-therapy groups [80]. Waitlist control groups are not an option because of cohort effects (different gestational age). In addition, the meta-analyses have typically limited their focus to one variable, for example, unintended pregnancy or partner violence. Other limitations have been frequently noted in earlier reviews including the samples not being representative, the research relying on self-reports, the confounding conditions and the need for multivariate research.

Although the samples of the recent studies appear to be significantly larger, they continue to be unrepresentative of prenatally depressed women who seek treatment including psychotherapy and antidepressants. Another limitation is the comorbidity of different emotional states including depression, anxiety and anger that confound the specific effects of prenatal depression. Given the difficulty of recruiting strictly depressed women, future studies might also include measures of anxiety as well as measures of anger, as that emotional state has also been documented for prenatally depressed women. Prenatal depression is also confounded by pre-pregnancy depression which is rarely assessed as a potentially confounding variable. Postpartum depression also confounds prenatal depression effects as many of the follow-up developmental variables are also affected by continuing depression into the postpartum period. The prenatal depression effects are further confounded by the probable genetic predispositions that are shared by the parents and their offspring. Surprisingly, research on the genetic determinants of prenatal depression and of prenatal depression effects has been rare.

Another limitation of the recent prenatal depression literature is the variability of measures and definitions of depression (different forms of depression and different diagnostic criteria) and the measurement of depression at different trimesters of pregnancy. Most of the studies have relied on self-report, especially the large sample longitudinal studies for which that might be expected [81-83]. Although the majority of the longitudinal studies exploring the effects of prenatal depression on developmental outcomes have used the EPDS, the intervention studies have more often used the CES-D. Dozens of studies highlight the psychometric properties of the EPDS, but the different CES-D subscales, for example, the negative affect and somatic/vegetative subscales, may be more informative of the different prenatal depression profiles.

Although there are some multivariate studies in the recent literature on prenatal depression, most of the studies have been univariate, especially the reports on large, longitudinal samples. These large, rich databases could likely be mined for other variables and, in turn, yield multivariate risk profiles based on regression or profile analyses. Multivariate risk profiles would likely be more informative, accurate screening measures than the depression scales alone. In addition, future laboratory studies may be more informative if multiple measures were taken. For example, in the study on withdrawal feelings of prenatally depressed women to distressed infant face images, saliva sampling for cortisol and alpha amylase and EEG measures may have provided more objective, confirmatory data for the self-reported withdrawal reactions by the prenatally depressed women. Despite these methodological limitations, this recent literature has highlighted more severe conditions that can result from prenatal depression as well as an increase in prenatal screening and interventions and the continuing need for more robust prenatal depression research.

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