Acute and Long-Term Behavioral Outcome of Infants and Children Exposed in Utero to Either Maternal Depression or Antidepressants: A Review of the Literature

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ABSTRACT

Objective: The authors reviewed the published literature on the acute and long-term neurobehavioral effects on infants and children of either in utero exposure to maternal depression or in utero exposure to antidepressants.

Data Sources: The PubMed electronic database was searched to locate 292 English-language studies from the first available year to October 2013 using the keywords *pregnancy*, *antidepressants*, *depression*, *perinatal*, and *neurobehavioral*.

Study Selection: The authors reviewed only prospective studies that assessed the impact of maternal depression during pregnancy or maternal antidepressant treatment during pregnancy on (1) clearly defined short-term behavioral outcomes in infants (perinatal outcome) or (2) longer-term behavioral outcomes in infants and children (neurodevelopmental outcome).

Data Extraction: Studies were included if they were prospective and assessed the impact of maternal depression or maternal antidepressant treatment during pregnancy on clearly measurable, objective short-term and longer-term behavioral outcomes in infants and children.

Results: Untreated depression during pregnancy is associated with short-term neonatal effects, including increased distress after delivery, less than optimal orientation and motor activity, and disrupted sleep. Longer-term effects on neurobehavioral outcome have also been reported, including disruptive social behavior, depression, and changes in the period of sensitivity for language discrimination. Antidepressant exposure during pregnancy is associated with adverse short-term perinatal symptomatology, including effects on autonomic and motor activity, habituation, and sleep. Longer-term studies of neurobehavioral outcomes of in utero antidepressant exposure suggest potential effects on gross motor function and language development but not cognition.

Conclusions: In utero exposure to either maternal depression or antidepressants carries risks to the developing fetus. Treatment decisions regarding whether and how to treat depression during pregnancy must be made on an individual basis, with careful consideration of the impact of these decisions on both mother and infant.

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While maternal psychological health during pregnancy has been a subject of interest for decades, only recently have studies focused on the effects of maternal depression on infant outcome. Active depressive symptoms entail significant risks to the mother, including poor nutrition; inadequate weight gain; poor prenatal care; cigarette, alcohol, or other substance use; and exposure to multiple medications.[1–3] These risks, in turn, can negatively impact the developing fetus and thus the outcome of the infant. In some cases, severe depression can lead to ambivalence toward, or even termination of, the pregnancy.[4]

As untreated depression may have adverse consequences, treatment of depression during pregnancy seems critical. However, consideration of treatment has highlighted the complicated nature of weighing the risk-benefit decision with respect to risks of untreated illness on the one hand and the known and unknown risks of fetal exposure to antidepressants on the other. Treatment of mild-to-moderate prenatal depression with psychotherapy has been shown to have beneficial effects on maternal outcome,[5] with no known harm to the fetus. For more severe symptoms, however, antidepressants may be considered.[6] Unlike other organ systems, the fetal brain continues to develop throughout pregnancy and can be impacted across gestation by exposure to antidepressants, which readily cross the placenta.[7] As a result, fetal exposure to antidepressants in utero may be associated with risks to the infant. For women with significant depressive symptoms, it is unclear whether maternal depressive symptoms or antidepressant medications would be more detrimental to the outcome of the infant. While quantification of relative risks is the obvious goal to make optimal treatment decisions, currently available data do not allow for such an exact calculation.

Despite 25 years of research, the effects of fetal exposure to maternal depression remain difficult to separate from those of fetal exposure to antidepressant medication. Ethical concerns limit randomized, placebo-controlled studies in gravid populations, and a study directly comparing the risks of fetal exposure to maternal depression in utero versus fetal exposure to antidepressant medications is unlikely to be undertaken. Clinicians must therefore rely on naturalistic studies of infant outcomes of women with untreated prenatal depression and women who receive treatment with antidepressants during pregnancy. Outcomes of particular

Clinical Points

- Prospective studies of the impact of in utero exposure to maternal depression or antidepressant treatment on clearly defined short- and long-term behavioral outcomes of infants and children are limited.
- The majority of existing studies to date do not suggest that in utero exposure to either maternal depression or antidepressant treatment has significant impact or major lasting sequelae on the neurobehavioral development of the child.
- Treatment decisions regarding maternal depression during pregnancy must be made on an individual basis, with careful consideration of the impact of treatment versus lack of treatment on both mother and child.

interest include (1) obstetrical outcomes such as prematurity or low birth weight of the neonate, (2) perinatal outcomes (those related to acute effects on the neonate shortly after delivery), and (3) neurobehavioral outcomes (those related to the longer-term neurodevelopment of the infant and child). As the impact of depression and antidepressants on obstetrical outcome has been extensively studied and reviewed,[8–10] and a recent study by Wisner et al[11] found no effect of in utero exposure to either major depression or selective serotonin reuptake inhibitors (SSRIs) on infant growth across the first year of life, the current review focuses on the effects of untreated maternal depression or antidepressant medication treatment during pregnancy on the perinatal and longer-term neurobehavioral outcome of the child. We undertook a comprehensive review of only the prospective literature to date with the hope that such a review might enable clinicians to help patients weigh risks of treated versus untreated depression on the developing fetus.

METHOD

The PubMed database was searched from the first available year to October 2013 using the keywords *pregnancy*, *antidepressants*, *depression*, *perinatal*, and *neurobehavioral*. This resulted in our finding 292 articles after limiting for English language. Studies were included in the current review according to the following a priori criteria for eligibility: (1) prospective studies that included women with depression, assessed the impact of maternal depression or maternal antidepressant treatment during pregnancy, reported in English, and were published in peer-reviewed journals; (2) participants aged 18 years or above, with symptoms of prenatal depression or prenatal treatment with antidepressants; studies of participants with prenatal depression were further assessed based on the use of formal diagnostic classification of depressive disorder versus dimensional measures of depressive symptoms; and (3) clearly measurable objective short-term behavioral outcomes in the infants (perinatal outcome) and longer-term behavioral outcomes in infants and children (neurodevelopmental outcome), as assessed prospectively with structured evaluations of infants and children. For the purposes of this review, short-term outcomes are operationalized as those assessed within the first 2 weeks of infant age and long-term follow-up is operationalized as follow-up of infants and children 6 weeks or older. Studies in which the sole outcome "measure" was neonatal intensive care unit or special care nursery admission or prolonged hospitalization were not included. Similarly, studies whose outcomes were based solely on parental report were not included. The methodological quality of each study was evaluated by one of the authors (R.S.) to ensure the reported study met the criteria. Variability in outcomes for the eligible studies precluded a meta-analysis of results. Animal studies on the effects of maternal depression or antidepressant exposure on fetal neurodevelopment and behavioral outcome are summarized for background information but are not included in the formal review itself.

IMPACT OF MATERNAL DEPRESSION DURING PREGNANCY ON PERINATAL AND NEURODEVELOPMENTAL BEHAVIORAL OUTCOME

Depression in Pregnancy: Short-Term Perinatal Outcome

Animal studies indicating that maternal stress changes the developing brain. Data from research on animals have shown that maternal stress at critical periods of development can affect programming of the fetal brain, with influences on neuronal differentiation and function at different stages of development that, depending on the amount and timing of stress, lead to changes in behavior, learning, and attention in the offspring. In the primate literature, offspring of rhesus monkeys stressed during gestation demonstrate anxiety in novel situations, with clinging, irritability, decreased exploration and social interaction, and impaired cognitive performance.[12] The impact of maternal stress on the fetus may partly be mediated through changes in blood flow, with constriction of placental arteries resulting in decreased fetal blood flow and transient hypoxia.[12] Additionally, a stress-induced rise in glucocorticoid levels can readily reach the fetal brain, causing activation of glucocorticoid receptors in the hippocampus, hypothalamus, cingulate cortex, and amygdala during development. With rapid growth and high turnover of neuronal connections, the fetal brain is especially vulnerable to hormones that reach it in excess. Such hormones can impede the formation of neural connections and reduce plasticity and neurotransmitter activity, causing subtle changes in cognitive function and behavior. Gestational stress in rats has been shown to increase levels of tryptophan, serotonin, and 5-hydroxyindoleacetic acid (5-HIAA)in the fetal brain until at least postnatal day 10,[13] suggesting changes in hypothalamic-pituitary-adrenal axis activity and behavior.

Human studies. Although not nearly as extensive as research in the animal world, the few human studies suggest that depression during pregnancy may affect infant perinatal or neurobehavioral outcome. To date, only 5 published studies[8,14–17] prospectively evaluated the impact of maternal depression during pregnancy on short-term (up to 2 weeks of age) perinatal outcome using structured

Table 1. Prospective Studies on Impact of Maternal Depression During Pregnancy on Short-Term Perinatal Outcome

Study	Sample Size	Design	Assessment	Findings	Comments
Field et al, 2007[15]	N = 253: 83 depressed, 170 nondepressed	Prospective, clinical diagnosis of depression, CES-D administered twice	Neonatal sleep at age 1 d	Increased sleep disturbance and less deep sleep in depressed compared to nondepressed group	Blinded assessments of infants were performed
Wisner et al, 2009[8]	N = 167[a]: 14 with continuous depression, 22 with partial depression, 131 controls	Prospective *DSM-IV* diagnosis of major depressive disorder. Severity assessed with SIGH-ADS. Depression course charted by month across pregnancy.	Peripartum Events Scale	No differences between groups	Blinded infant assessments. Data on smoking and alcohol use included. Exclusion of women with active substance use disorder or benzodiazepine exposure. Assessment of mood across pregnancy.
Marcus et al, 2011[17]	N = 140: 8% with increased depression on BDI	Prospective BDI at 28, 32, 37 wk	NNNS at age 2 wk	Greater hypotonicity and more rapid habituation to auditory and visual stimuli	Examiners blinded to maternal depression status
Field et al, 2001[14]	N = 120: 80 depressed, 40 nondepressed	Prospective, single CES-D rating	BNBAS, sleep at age 1 d	Decreased habituation, orientation, and motor performance on BNBAS and increased indeterminate or uncodable sleep in depressed compared to nondepressed group	Blinded assessments of infants were performed
Lundy et al, 1999[16]	N = 63: 36 depressed, 27 nondepressed	Prospective, single assessment of depression with CES-D	BNBAS at age < 1 wk	Decreased orientation, abnormal reflexes and suboptimal scores on excitability and withdrawal factors in depressed compared to nondepressed groups	Blinded assessments of infants were performed

[a]Only relevant exposure groups included.
Abbreviations: BDI = Beck Depression Inventory, BNBAS = Brazelton Neonatal Behavioral Assessment Scale, CES-D = Center for Epidemiologic Studies Depression Scale, NNNS = Neonatal Intensive Care Unite Neurobehavioral Scale, SIGH-ADS = Hamilton Depression Rating Scale with Atypical Depression Supplement.

newborn assessments (Table 1). These studies vary widely in samples sizes ranging from 63 to 253 and include a total of 246 women with depressive symptoms and 497 women without depressive symptoms during pregnancy.

Of the 5 prospective studies, only 2 studies[8,15] included women with a formal clinical diagnosis of depression. In one study[15] of 253 pregnant women not on antidepressant medications and evaluated in the second trimester of pregnancy, 83 women were found to meet criteria for a Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID)[18] diagnosis of depression while 170 women were assigned to a nondepressed group. Follow-up mean ± SD depression scores, assessed with the Center for Epidemiologic Studies Depression Scale (CES-D),[19] were 21.9 ± 9.7 for the depressed group and 9.5 ± 5.5 in the nondepressed group. Infants were evaluated shortly after birth by trained, blinded researchers. Neonates of the depressed group demonstrated a lower percentage of time in deep sleep, a greater percentage of sleep time in indeterminate or disturbed sleep, significantly greater disturbance of sleep, and increased crying and fussiness. Strengths of this study include maternal diagnostic evaluations for depression and blinded infant assessments, while limitations include the lack of information regarding potential confounding factors such as maternal substance use during pregnancy. Wisner et al[8] reported neonatal outcomes for 36 women with a *DSM-IV* Axis I (SCID) diagnosis of major depressive disorder and either continuous depression throughout pregnancy (n = 14, Structured Interview Guide for the Hamilton Depression Rating Scale, Atypical Depression Symptoms version [SIGH-ADS] score = 23.9 ± 3.7) or partial depression during pregnancy (n = 22, SIGH-ADS score = 16.6 ± 6.8) with the Peripartum Events Scale.[20] Outcomes did not differ between infants exposed to depression versus unexposed control infants or those exposed to SSRIs. Strengths of this study include assessment of depression across pregnancy, blinded outcome assessments, and exclusion of women with an active substance use disorder or benzodiazepine use.

Two other prospective studies[14,16] used a single assessment with the CES-D to categorize subjects with or without depressive symptoms during pregnancy and evaluated infants with the Brazelton Neonatal Behavioral Assessment Scale (BNBAS).[21] Field et al[14] assessed the infants of 80 pregnant women with depressive symptoms (mean CES-D score = 24.9) and 40 nondepressed women (mean CES-D score = 8.2) at the first ultrasound visit. Newborns of the depressed group had more indeterminate, uncodable sleep patterns after delivery and performed less optimally on the habituation, orientation, and motor clusters of the BNBAS. Infant raters were blinded to maternal depression status. Information regarding potential confounds such as substance use was not included. In an earlier study that also used the BNBAS, Lundy et al[16] assessed neonates of 36 women with depression (CES-D scores > 16) and 27 women without depression (CES-D scores < 12) in the third trimester of pregnancy. The authors excluded women with substance use during pregnancy. The BNBAS was administered to infants within 1 week of birth by trained researchers blind to group classification. Infants of depressed mothers had lower orientation scores, more abnormal reflexes, and less optimal scores on excitability and withdrawal measures than the infants of the nondepressed group.

Marcus et al[17] followed 140 women and found that infants of mothers with elevated depressive symptoms on

Table 2. Prospective Studies on Impact of Maternal Depression in Pregnancy on Long-Term Neurodevelopmental Behavioral Outcome

Study	Sample Size	Design	Assessment	Findings	Comments
Tse et al, 2010[26]	N = 1,030: 81 mothers with EPDS score ≥ 13 in mid-pregnancy	Prospective	PPVT; WRAVMA at age 3 y	No difference in child cognition scores between depressed and nondepressed groups after adjustment of sociodemographic factors	Depression symptoms were measured at a single time point, infant assessments were performed by masked examiners, and data were collected on cigarette and alcohol use in pregnancy and mood at 6 mo postpartum
Pearson et al, 2013[29]	N = 2,847: depression assessed with EPDS	Prospective	Adolescent depression in offspring measured with CIS-R at age 18 y	Offspring 1.28 times (95% CI, 1.08–1.51; $P = .003$) more likely to have depression at age 18 y for each standard deviation increased in maternal score antenatally	Findings independent of later maternal depression. Study included repeated measures of maternal depression, paternal depression, and data on smoking, breastfeeding, and nonparental child care.
Nulman et al, 2012[27]	N = 240: 54 with untreated depression diagnosed per *DSM-IV* criteria	Prospective	Wechsler Preschool and Primary Scale of Intelligence–Third Edition at ages 3–7 y	No significant differences between depressed and nondepressed groups	Study controlled for maternal mood state during pregnancy and at the time of child assessment. Infant assessments performed by masked examiners. Minimal and comparable alcohol and cigarette use among subjects in groups.
Hay et al, 2010[25]	N = 120: 38 with *ICD* diagnosis of depression in pregnancy	Prospective. Depression assessed with CIS twice in pregnancy	Diagnosis of conduct disorder by ages 11 or 16 y; arrest by age 16 y	Increased risk for adolescent antisocial outcomes in depressed group	Study controlled for prenatal cigarette and alcohol use, family environment, recurrent depression exposure, and parents' antisocial behavior
DiPietro et al, 2006[24]	N = 94: depression assessed at 24 wk with the depression subscale of the shortened POMS; CES-D at 32 wk	Prospective	Bayley Scales of Infant Development–II at age 2 y	Higher scores on depression and anxiety subscales of POMS associated with increased scores on MDI and PDI subscales of Bayleys	Study included subjects with healthy uncomplicated pregnancies. No information included on cigarette use, substance use, or postpartum mood.
Weikum et al, 2012[28]	N = 85: 21 with untreated depression	Prospective	Hindi sound discrimination and visual language discrimination at age 6 and 10 mo	Unreliable discrimination at 6 mo, reliable discrimination at 10 mo, and delayed stable discrimination in depressed group	Study included assessment of maternal mood during pregnancy and in postpartum. Minimal alcohol and cigarette use by subjects.

Abbreviations: CES-D = Center for Epidemiologic Studies Depression Scale, CIS = Clinical Interview Schedule, CIS-R = Clinical Interview Schedule-Revised, EPDS = Edinburgh Postnatal Depression Scale, MDI = Mental Development Index, PDI = Psychomotor Development Index, POMS = Profile of Mood States, PPVT = Peabody Picture Vocabulary Test, WRAVMA = Wide Range Achievement of Visual Motor Abilities.

the Beck Depression Inventory (BDI)[22] during pregnancy were more hypotonic at 2 weeks of age when compared to infants of mothers with low and/or intermediate levels of depressive symptoms, suggesting effects on neurobehavioral development. However, the infants of mothers with depressive symptoms also habituated more quickly to auditory and visual stimuli. A strength of this study was the use of the structured Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS)[23] to assess infants.

In summary, 5 prospective studies[8,14–17] have been published that assess the association of maternal depression during pregnancy and short-term perinatal outcome. These studies in total included 743 pregnant subjects, 33% of whom had depressive symptoms during pregnancy. Only 2 of these studies[8,15] utilized formal diagnostic evaluations for maternal depression during pregnancy. The remaining 3 studies included maternal depressive symptoms based on rating scales, a limitation that can result in misdiagnosis because conditions such as anxiety or substance abuse can cause elevated scores that do not represent depression. Nevertheless, these prospective studies suggest that untreated maternal depression during pregnancy may have short-term effects on early infant sleep, orientation, and motor activity. Further prospective studies with larger sample sizes of women with clearly diagnosed depressive disorder and the exclusion of confounding factors such as substance use are warranted.

Depression in Pregnancy: Longer-Term Neurodevelopmental Behavioral Outcome

Prospective studies on the impact of maternal depression during pregnancy on infant and child neurodevelopment are also limited. Six prospective studies (Table 2) have been published to date[24–29] with sample sizes ranging from 85 to 2,847 subjects and follow-up times ranging from 6 months to 18 years. Additionally, outcome measures varied from structured developmental assessments (eg, the Bayley Scales of Infant Development),[24,30] cognitive evaluations with the Wechsler Preschool and Primary Scale of Intelligence–Third Edition,[27,31] tests of auditory discrimination,[28] and assessment of psychiatric disorders utilizing the Child and Adolescent Psychiatric Assessment[25,32,33] and the Clinical Interview Schedule-Revised (CIS-R).[29,34]

Only 2 prospective studies[25,27] of the 6 included women with a diagnosis of depression, as opposed to depressive symptomatology during pregnancy, and are discussed first. Hay et al[25] followed 120 British adolescents and their parents, looking at outcomes of older children. Maternal

depression during pregnancy, diagnosed in 38 of the mothers by the Clinical Interview Schedule, a standardized clinical interview for use in community surveys,[35] significantly predicted subsequent violence and antisocial behavior in the adolescents. Strengths of this study included formal maternal psychiatric diagnoses, objective and clearly defined child outcomes, and control of confounding variables such as family environment, childhood exposure to maternal depression, cigarette and alcohol use during pregnancy, and parental antisocial behavior. However, women who were depressed in pregnancy reported a history of significantly more juvenile conduct symptoms themselves than those without depression. A recent study by Nulman et al[27] found that full-scale, verbal, and performance IQ scores were not significantly different for children, assessed between 3 and 7 years of age, of 54 women with untreated *DSM-IV* criteria depression during pregnancy compared to those of 62 control women. In this study, the presence of postpartum depression did not impact group IQ differences years later.

Four[24,26,28,29] of the 6 prospective studies on infant and child neurodevelopment assessed maternal depression exposure with rating scales of depressive symptoms. An innovative recent study by Weikum et al[28] examined infant language development utilizing auditory discrimination of nonnative consonant speech sound contrast and visual discrimination of the change from one language to another while watching silent talking faces in babies at 6 and 10 months of age. Normally, infants are able to discriminate auditory and visual language signs at 6 months but typically not as late as10 months of age, indicating a critical period of sensitivity in language development. The study authors found that 16 infants of mothers with depression during pregnancy showed unreliable discrimination at 6 months and reliable discrimination at 10 months of age, suggesting a delay in the window of sensitivity to nonnative language distinctions. The authors caution that the impact of prenatal versus postnatal maternal mood, assessed with the Hamilton Depression Rating Scale (HDRS),[36] remains to be determined. In a study with much longer offspring follow-up, Pearson et al[29] found that antenatal depression, measured prospectively with the Edinburgh Postnatal Depression Scale,[37] was an independent risk factor for depression in the offspring at 18 years of age (odds ratio = 1.28; 95% CI, 1.08–1.51; $P = .003$). Strengths of this study included large sample size, repeated measures of maternal depression, and inclusion of confounding and moderating variables including smoking, breastfeeding, nonparental childcare, and paternal depression.

In contrast to these 2 studies[28,29] suggesting adverse effects of depression exposure on infant neurodevelopment, a study of 1,030 mother-child pairs by Tse et al[26] found no impact of maternal depression on child cognition as assessed with structured tests of vocabulary and visual motor activities. Among 81 women with elevated midpregnancy depression scores on the Edinburgh Postnatal Depression Scale,[37] maternal depressive symptoms were not associated with effects on childhood cognition at 3 years of age after adjustment for sociodemographic variables.

Interestingly, DiPietro et al[24] found that elevated symptoms of maternal anxiety and depression during pregnancy, assessed with the Profile of Mood States (POMS),[38] were associated with higher scores, indicating more optimal development, on the motor and mental development subscales of the Bayley Scales of Infant Development–II for 94 toddlers evaluated at 2 years of age. The authors suggested that mild-to-moderate levels of psychological stress during pregnancy may enhance fetal maturation. Of note, this study's population included healthy, financially stable women with subclinical levels of depression, and the authors caution that their findings may not generalize to women with external stressors or clinical levels of depression and anxiety.

In summary, 6 prospective studies[24–29] have followed infants and children of 4,416 women from 6 months to 18 years of age. Some of these studies suggest that untreated prenatal depressive symptoms may have an untoward impact on the neurodevelopment of the child. However, only 2 of these studies utilized formal diagnostic criteria to determine maternal depression exposure during pregnancy. The most comprehensive of these studies[27] found no significant behavioral differences in children with mothers who were depressed versus not depressed in pregnancy. Clearly, these are difficult studies to perform. The main concerns reported include a possible delay in the critical period of sensitivity to nonnative language discrimination and increased child and adolescent behavioral difficulties and adolescent depression for the offspring of women with depression during pregnancy.

IMPACT OF ANTIDEPRESSANTS ON PERINATAL AND NEURODEVELOPMENTAL BEHAVIORAL OUTCOME

Animal Studies

Animal data regarding gestational antidepressant exposure on offspring outcome are more limited. However, animal models have shown that in utero antidepressant exposure can cause early changes in serotonergic tone with molecular, neuroanatomical, and functional consequences.[13] SSRIs block the serotonin transporter (5-HTT), raising extracellular serotonin levels, which regulate cognition, attention, emotion, learning, sleep, arousal, and stress in the mature brain. High central serotonin levels during development in mice have shown permanent axonal connection deficits in the somatosensory cortex and the lateral geniculate nucleus throughout life.[13] Early injection of fluoxetine in neonatal rats has shown long-lasting effects on the function and structure of the somatosensory system.[13] In rodents, a developmental increase in serotonin levels or exposure to 5-HTT–blocking drugs in the early postnatal period reduces novelty investigation behavior and increases anxiety, sleep anomalies, anhedonia, and a helpless state when exposed to stress.[13] Such findings in animal models suggest that early changes in serotonergic tone have molecular, neuroanatomical, and functional consequences that are dependent on the timing, or critical periods, and direction, increased or decreased, of change.

Table 3. Prospective Studies of Impact of Antidepressant Exposure on Short-Term Perinatal Outcome

Study	Sample Size	Design	Assessment	Findings	Comments
Wisner et al, 2009[8]	N = 202[a]: 48 continuous SSRI exposure, 23 partial SSRI exposure, 131 no SSRI or depression exposure	Prospective	Peripartum Events Scale	No differences between groups	Antidepressant exposure confirmed through blood sampling. Data on smoking and alcohol use collected. Blinded infant assessments.
Levinson-Castiel et al, 2006[42]	N = 120: 60 SSRI exposed in third trimester or more; 60 controls	Prospective assessment of infants identified at delivery	Neonatal abstinence syndrome assessed with Finnegan score	30% of SSRI-exposed infants had neonatal abstinence syndrome	Infant assessments were not performed by blinded examiners. Study did not include confirmation of antidepressant exposure or data on maternal psychiatric symptoms.
Rampono et al, 2009[39]	N = 56: 38 SSRI/SNRI exposed, 18 controls	Prospective	Finnegan NAS; BNBAS	NAS scores were higher for exposed vs control infants on day 1 ($P = .05$). BNBAS scores for habituation, social-interactive, and motor and autonomic clusters were greater in exposed infants ($P < .05$).	Infant assessments performed by blinded examiners. Study included confirmation of antidepressant exposure. EPDS scores during pregnancy were comparable between groups.
Laine et al, 2003[43]	N = 40: 20 with citalopram or fluoxetine exposure, 20 controls	Prospective	Assessment of serotonergic symptoms in the infant (blood pressure, heart rate, temperature, myoclonus, restlessness, tremor, shivering, hyperreflexia, incoordination, rigidity)	4-Fold increased symptoms in first 4 d in SSRI-exposed group ($P = .008$) and lower cord 5-HIAA in SSRI group ($P = .02$)	Study included confirmation of antidepressant exposure by blood levels. Infant assessments were not consistently performed by blinded examiners. Data on maternal psychiatric symptoms were not included.
Zeskind and Stephens, 2004[40]	N = 34: 17 SSRI exposed, 17 nonexposed	Prospective assessment of infants; mothers identified at delivery	Behavioral state, startles, tremulousness, motor activity, HRV	SSRI infants were more motorically active and tremulous with less complexity in HRV, fewer changes in behavioral state, fewer different behavioral states, lower peak behavioral state, and more REM sleep. The effects for tremulousness and all measures of state and sleep organization remained after covarying for gestational age.	Study included infant assessments by blinded examiners. Information on duration, timing, and dosage of antidepressant or maternal psychiatric symptoms was not included. Confirmation of antidepressant use was not included.
ter Horst et al, 2012[41]	N = 10: exposed to clomipramine	Prospective	Finnegan score; symptoms of withdrawal	Mean Finnegan score was elevated up to 48 h postpartum. Infants demonstrated decreased sleep (n = 6), poor feeding (n = 3), tremors (n = 6), increased Moro (n = 3), increased respirations (n = 3), tachycardia and cyanosis (n = 2).	Study did not exclude for nicotine and alcohol use. Information on whether infant assessments were performed by blinded examiners was not included. Antidepressant exposure was confirmed through blood sampling.

[a]Only relevant exposure groups included.
Abbreviations: BNBAS = Brazelton Neonatal Behavioral Assessment Scale, EPDS = Edinburgh Postnatal Depression Scale, 5-HIAA = 5-hydroxyindoleacetic acid, HRV = heart rate variability, NAS = Neonatal Abstinence Score, REM = rapid eye movement, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Antidepressants During Pregnancy and Short-Term Perinatal Outcome

Over the past decade, there have been multiple reports in the human literature and lay public information regarding the potential adverse impact of in utero antidepressant exposure on the perinatal outcome of the infant. Few of these reports included prospective studies and most varied greatly on method of assessment and outcome measures. The 6 prospective studies[8,39–43] to date (Table 3), with structured infant assessments, included sample sizes of antidepressant-exposed subjects ranging from 10 to 71 and outcomes that included measures of neonatal abstinence syndrome and performance on the BNBAS. These studies reviewed below together included 216 subjects with antidepressant exposure and 246 without, and the majority suggest that antidepressant exposure, at least in the third trimester, may be associated with adverse short-term perinatal symptomatology.

A prospective study by Rampono et al[39] utilized the Finnegan scale,[44] a systematic, objective instrument that quantifies neonatal abstinence symptoms, to assess outcomes for 38 infants exposed to SSRI or serotonin-norepinephrine reuptake inhibitor antidepressants and 18 unexposed infants. Maximum neonatal abstinence scores (NAS) were significantly greater on postpartum day 1 for the exposed versus the unexposed infants. Remaining NAS scores up to 3 days postpartum were comparable, however, suggesting that any effects of antidepressants on measures of abstinence were transient. Infant evaluations with the BNBAS performed by blinded raters on postpartum day 3 found lower scores on habituation, social-interactive, motor, and autonomic clusters for exposed versus unexposed babies, suggesting less optimal functioning in these areas. Of note, though not statistically significant, scores on the Edinburgh Postnatal Depression Scale were higher and twice as many women used alcohol

during pregnancy in the antidepressant group compared to the control group.

Zeskind and Stephens[40] also used blinded BNBAS assessments for 17 SSRI-exposed neonates who demonstrated greater motor activity and tremulousness, less complexity in heart rate variability, fewer changes in behavioral state, and more rapid eye movement sleep compared to nonexposed neonates at 39 hours after delivery. Differences in tremulousness and measures of state and sleep organization remained even after covarying the effects of gestational age at birth. Whether these symptoms were transient or had persistent effects in the neonate over time is not known. Limitations of this study included lack of information on depressive symptoms during pregnancy and the inclusion of 4 women with prenatal marijuana use in the SSRI group.

A recent small study[41] examined the neonates of 10 mothers treated with clomipramine for the entire pregnancy. Mean Finnegan scores were elevated up to 48 hours postpartum. All but one infant had at least one symptom of withdrawal including decreased sleep, poor feeding, tremors, increased Moro reflex, increased respirations, tachycardia, and cyanosis. Information regarding maternal mood during pregnancy was not included, and women with nicotine or alcohol use were not excluded. Levinson-Castiel et al[42] also used the Finnegan scale[45] in 60 SSRI-exposed and 60 nonexposed infants. Symptoms of neonatal abstinence were present in 30% of neonates exposed to SSRIs in utero. Results for this study were limited by nonblinded infant examinations and lack of information regarding maternal mood during pregnancy.

In contrast to possible withdrawal from SSRIs, symptoms in the baby could represent serotonergic central nervous system (CNS) adverse effects. In a study by Laine et al,[43] serotonergic symptoms in SSRI-exposed infants were inversely correlated with cord blood 5-HIAA concentrations, consistent with the literature that lower cerebrospinal fluid concentrations are reflective of SSRI-induced increase in CNS serotonergic activity. Given the high rate of placental passage of antidepressants, it is feasible that neonates could experience adverse effects of these medications.[7,46]

Unlike studies reporting adverse short-term outcomes with antidepressant exposure, Wisner et al[8] found no differences in scores on the Peripartum Events Scale[20] between 71 infants exposed to SSRIs in utero (48 with continuous exposure) compared to 131 control unexposed infants or those infants exposed to depression.

In summary, of the 6 prospective studies[8,39–43] involving 462 pregnant women, 47% of whom were treated with antidepressants, 5 studies[39–43] strongly suggest that antidepressant exposure, at least in the third trimester of pregnancy, may be associated with adverse perinatal symptomatology, including effects on autonomic and motor activity, habituation, and sleep. Unfortunately, limitations of these studies include the lack of control for maternal mood and substance use during pregnancy, and thus the degree to which these variables contribute to neonatal behavior is difficult to determine. Future studies, with larger sample sizes, the inclusion of untreated depressed subjects as well as euthymic subjects treated with antidepressants, and the exclusion of substance use, are warranted in order to clearly delineate the impact of antidepressant exposure on the perinatal outcome of the neonate. Additionally some infants may have a greater susceptibility to perinatal symptoms, and evaluations of genomic differences in mothers and infants may help to elucidate factors that modulate vulnerability to short-term adverse outcomes.[47]

IN UTERO ANTIDEPRESSANT EXPOSURE AND LONG-TERM BEHAVIORAL NEURODEVELOPMENTAL OUTCOME

Thus far, 13 prospective studies[27,28,48–58] utilizing structured assessments of behavior and cognition (Table 4) have been published that report neurodevelopmental outcomes for infants exposed to antidepressants during pregnancy. These prospective studies have included sample sizes ranging from 22 to 202 exposed infants, a nonexposed control group in the majority of studies, and a range of follow-up of up to 7 years. While 9 studies[27,48–50,53,55–58] found no significant effects of antidepressant exposure on the offspring, 4 studies[28,51,52,54] suggest potential effects on gross motor function, behavior, and language development.

Nulman et al[27] compared cognitive outcomes from 3 to 7 years of age on the Wechsler Preschool and Primary Scale of Intelligence–Third Edition[31] for 62 children exposed to SSRIs during pregnancy, 62 children exposed to venlafaxine during pregnancy, 54 children of mothers with untreated depression during pregnancy, and 62 children of healthy controls. After controlling for confounding variables, neither group membership nor dose and duration of antidepressant treatment during pregnancy significantly predicted cognitive outcomes. Strengths of this study include its design with the inclusion of both women with untreated depression and healthy controls and its control for severity of maternal depression during pregnancy and at the time of child assessment. In 2 earlier studies by Nulman et al[48,49] of children assessed between 15 and 86 months of age who had been exposed to SSRIs and tricyclic antidepressants in the first trimester (n = 63 and 80, respectively)[49] and throughout pregnancy (n = 46 and 40, respectively),[48] scores on global IQ, language development, and behavioral IQ on the Bayley Scales of Infant Development,[30] the McCarthy Scales of Children's Abilities,[59] and the Reynell Developmental Language Scales[60,61] were comparable to unexposed controls. Weikum et al[56] also found no significant differences on the Bayley Scales of Infant Development at 6 months of age for 30 infants exposed to SSRIs in utero compared to 43 unexposed infants. Similarly, Johnson et al[58] found no significant differences at 6 months of age on the Infant Neurologic International Battery (INFANIB)[62] between 202 infants exposed to antidepressants in pregnancy and 85 unexposed infants.

A study by our group[50] compared outcomes at 1 week and 6–8 weeks of age for 33 infants exposed to antidepressants in utero, 16 infants of mothers with a history of depression without antidepressant exposure or with minimal exposure in

Table 4. Prospective Studies of Impact of Antidepressant Exposure on Long-Term Neurodevelopmental Behavioral Outcome

Study	Sample	Design	Assessment	Findings	Comments
Johnson et al, 2012[58]	N = 287: antidepressant (n = 202), no antidepressant (n = 85; 32 of these with no psychiatric history)	Prospective	INFANIB, infant habituation	No significant differences between infants exposed to antidepressants compared to infants without exposure	Blinded infant assessments. Women with active substance use disorder excluded. 62% of control group had psychiatric history. 58 women in antidepressant group took other psychotropic medications. 45% of control group recruited after pregnancy.
Nulman et al, 2012[27]	N = 240: SSRIs (n = 62); venlafaxine (n = 62); depression, no antidepressants (n = 54); controls (n = 62); ages: 3 to 7 y	Prospective	Wechsler Preschool and Primary Scale of Intelligence–Third Edition	No significant differences between groups after controlling for covariates	Maternal mood assessed during pregnancy and at follow-up. Blinded infant assessments. Minimal alcohol or cigarette use among subjects.
Nulman et al, 1997[48]	N = 227: fluoxetine (n = 63), TCA (n = 80), healthy (n = 84); ages: 16–86 mo	Prospective	Bayley, McCarthy Scales, Reynell Developmental Language Scales	No evidence of adverse antidepressant impact	18 Fluoxetine and 36 TCA subjects enrolled in both studies
Nulman et al, 2002[49]	N = 122: fluoxetine (n = 46), TCA (n = 40), healthy (n = 36); ages: 15–71 mo	Prospective	Bayley, McCarthy Scales, Reynell Developmental Language Scales	No evidence of adverse antidepressant impact	18 Fluoxetine and 36 TCA subjects enrolled in both studies
Weikum et al, 2012[28]	N = 85: SSRIs (n = 32), depressed (n = 21), controls (n = 32); ages: 6 and 10 mo	Prospective	Auditory discrimination of nonnative consonant speech sound contrast and visual language discrimination at 6 and 10 mo	Failure to discriminate at 6 and 10 mo in SSRI group, suggestive of accelerated development of speech perception.	Maternal mood assessed in pregnancy and at follow-up. Minimal alcohol and cigarette use among subjects.
Weikum et al, 2013[56]	N = 73: SSRIs (n = 30), controls (n = 43); age: 6 mo	Prospective	Bayley Scales of Infant Development	No differences between groups.	Maternal mood assessed at 33 wk pregnancy and 3 mo postpartum. Minimal alcohol and cigarette use among subjects.
Suri et al, 2011[50]	N = 64: antidepressants (n = 33); depression, no antidepressants (n = 16); nonpsychiatric controls (n = 15); ages: 1 wk and 6–8 wk	Prospective	BNBAS	No significant difference in summary scores for the 7 major clusters of BNBAS between 3 groups	Homogeneous sample with women who were educated, married, and had early prenatal care
Reebye et al, 2002[53]	N = 61: SSRI (n = 24), SSRI + clonazepam (n = 14), healthy (n = 23); age: 3 mo	Prospective	Parent-Child Early Relational Assessment Scale	In SSRI + clonazepam group: positive infant affect negatively related to maternal negative affect; negative infant affects was positively related to maternal positive affect and negatively related to maternal negative affect. No differences between infants exposed to SSRIs alone and controls.	Videotapes analyzed by masked research assistant.
Oberlander et al, 2004[57]	N = 69: SSRI (n = 28), SSRI + clonazepam (n = 18), healthy (n = 23); ages: 2 and 8 mo	Prospective	Bayley	No differences between groups	Same cohort of infants/children
Misri et al, 2006[55]	N = 36: SSRI (n = 13), SSRI + clonazepam (n = 9), healthy (n = 14); ages: 48–60 mo	Prospective	Internalizing behaviors—Child-Teacher Report, CBCL	No differences between groups	Same cohort of infants/children
Oberlander et al, 2007[54]	N = 36: SSRI (n = 13), SSRI + clonazepam (n = 9), healthy (n = 14); ages: 48–60 mo	Prospective	Externalizing and attentional behaviors—CBCL, Wechsler IQ, laboratory assessment	No differences between groups. Persistence score for child behavior lower in SSRI group.	Same cohort of infants/children
Casper et al, 2011[51]	N = 55: SSRI exposure of varying durations; ages: 12–40 mo	Prospective	Bayley Scales of Infant Development–II	Longer duration of SSRI exposure in pregnancy associated with increased risk of lower PDI and BRS scores	Subjects had good prenatal care. Child assessments by blinded evaluators. Confound with depressive symptoms in pregnancy. Alcohol use in 5 women. 17 women recruited after delivery.
Casper et al, 2003[52]	N = 44: SSRI (n = 31), MDD/no medications (n = 13); ages: 6–40 mo	Cross-sectional	Bayley	SSRI decreased psychomotor	Some women enrolled after delivery

Abbreviations: BNBAS = Brazelton Neonatal Assessment Scale, BRS = Behavior Rating Scale, CBCL = Child Behavior Checklist, INFANIB = Infant Neurologic International Battery, MDD = major depressive disorder, PDI = Psychomotor Development Index, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

pregnancy, and 15 healthy controls. Infants were evaluated with the BNBAS with no significant differences in summary scores for the 7 major clusters of the BNBAS. Strengths of this study include monthly assessments of maternal mood and antidepressant use across pregnancy, the exclusion of subjects with substance use, and infant assessments performed by blinded raters.

In contrast to studies that did not find adverse effects of antidepressants on neurodevelopment, Casper et al[51] found that longer duration of SSRI exposure in pregnancy among 55 women with major depressive disorder (MDD) who were treated with SSRIs for varying durations was associated with lower psychomotor development index and behavioral rating scale scores on the Bayley Scales of Infant Development–II.[30] Children were assessed between 12 and 40 months of age. Maximum BDI scores during pregnancy were similar between children with SSRI exposure in the first trimester compared to second or third trimester exposure and exposure throughout pregnancy, and depression scores were comparable at postpartum follow-up. However, the authors caution that lack of frequent maternal mood assessments during pregnancy limits the ability to determine the effects of depression severity on child outcome. Strengths of this study include blinded assessments of children and good prenatal care of the mothers during pregnancy. In an earlier study, Casper et al[52] compared 31 infants with SSRI exposure during pregnancy with 13 infants of mothers with MDD who were not treated with medications during pregnancy. While the Bayley mental developmental scores were comparable for 6 and 40 months of age, the Bayley psychomotor development scores and the motor quality factor of the Bayley behavioral rating scales were significantly lower in the SSRI-exposed children. The authors conclude that SSRI exposure in utero may have subtle effects on motor development and motor control.

A study by Reebye et al[53] reported similar patterns of affect expressivity at 3 months of age on blinded assessments of parent-infant interaction utilizing the Parent-Child Early Relational Assessment[63] for a cohort of 24 SSRI-only exposed compared to 23 control infants. Results of further developmental assessments with the Bayley Scales of Infant Development at 2 and 8 months of age were not significantly different between groups.[57] Oberlander et al[54] subsequently reexamined these children at 4 years of age utilizing a procedure developed by Crowell and Feldman[64] to determine whether prenatal SSRI exposure was associated with altered activity levels. The persistence score for child behavior was significantly lower in the SSRI-exposed group, even after controlling for maternal mood, while scores on movement, aggressiveness, attention, and emotion were not significantly different between exposed and unexposed groups. Mean aggressiveness composite scores were significantly higher in those children with a history of poor neonatal adaptation associated with SSRI exposure, compared to children without a history of these symptoms. Strengths of this study include confirmation of antidepressant use with umbilical cord antidepressant measurement and control for maternal depressed mood at the time of follow-up. Misri et al[55] evaluated these children at 4 to 5 years of age and found that the 22 SSRI-exposed children were not more likely to be emotionally reactive, depressed, anxious, or withdrawn than the 14 unexposed control children, as assessed with the Crowell procedure.

In a recent novel study, Weikum et al[28] examined language development in 32 infants with prenatal SSRI exposure utilizing auditory discrimination of nonnative consonant speech sound contrast and visual discrimination of the change from one language to another while watching silent talking faces at 6 and 10 months of age. SSRI-exposed infants demonstrated failure to discriminate nonnative vowel and visual language changes that persisted at 10 months of age, supporting an accelerated timing of perceptual attunement when compared to control subjects. These findings were in opposition to the delay observed in infants of mothers with untreated maternal depression in pregnancy. Postpartum maternal mood at the time of infant assessment was controlled by adding maternal HDRS scores as a covariate. However, both mothers with prenatal antidepressant treatment and those with untreated depression had significantly higher levels of depression, assessed with the HDRS, during pregnancy compared to the control mothers.

In summary, 13 prospective studies[27,28,48–58] have assessed neurobehavioral infant outcome after in utero antidepressant exposure for 728 infants. The majority of these studies do not suggest major long-term adverse effects of prenatal antidepressant exposure on infant and child neurobehavioral development. The longest follow-up has been up to 7 years,[27] and no significant differences in neurobehavior have been found in antidepressant-exposed versus -unexposed children. While these negative results are encouraging with respect to the use of antidepressants during pregnancy, sample sizes have been small, and there are reports of possible subtle effects on gross motor function and language development, as well as potential longer-term consequences for children with a history of SSRI-associated poor neonatal adaptation. Most studies do not quantify the severity of depressive symptoms in mothers across pregnancy, so it is difficult to delineate the impact of pharmacologic treatment of depression versus depression itself on the long-term neurodevelopment of the child. Future large-scale studies should include control groups of women with untreated depression as well as healthy controls (as in the studies by Nulman et al[27] and Suri et al[50]).

CONCLUSIONS AND TREATMENT RECOMMENDATIONS

The current review of the literature, with its limitations discussed, suggests that the adverse effects of exposure to untreated active symptoms of maternal depression during pregnancy may increase vulnerability to infant distress shortly after delivery. Research from the animal literature has shown that maternal stress at critical periods of development can affect the programming of the fetal brain and subsequently lead to depressive-like behavior, anxiety, and learning and attention deficits in the offspring in rats and primates. While

potential effects on child and adolescent behavior[25] and mood[29] have been reported, prospective studies have not demonstrated definitive or clear long-term neurobehavioral sequelae.

Review of the antidepressant literature indicates that antidepressant exposure during pregnancy can also have adverse short-term perinatal effects, though findings are limited by potential confounds with maternal depression and/or substances. A review of the literature by Moses-Kolko et al[65] found that paroxetine and fluoxetine are most commonly associated with such adverse effects. The authors suggest that the half-lives of these antidepressants may play a role, with the short half-life of paroxetine contributing to withdrawal and the long half-life of fluoxetine contributing to toxicity. The majority of the 11 long-term studies of infants and children exposed to antidepressants in utero, however, do not show lasting adverse sequelae on neurodevelopment, including cognition and emotionality. While some reports suggest subtle longer-term changes on gross motor function and potential longer-term effects on language development, the clinical significance of these findings is not clear.

With risks of fetal exposure to maternal depression on the one hand versus risks of antidepressant exposure on the other, and the absence of a clear, evidence-based treatment algorithm, clinicians and patients are faced with the realization that no decision is risk-free, even when relying on the most up to date, evidence-based literature. Decisions whether to treat with antidepressants during pregnancy must be made on an individual basis, and patients presented with the same information may make different choices as a function of the relative weight ascribed to the various data on both sides of the risk-benefit analysis. In many cases of mild-to-moderate depression, psychotherapy can be a sole, effective modality for the treatment of depression during pregnancy.[5] For more severe symptoms, careful consideration should be given to the impact of a woman's depression on her ability to care for herself, as well as its impact on her family, care for other children, marriage, occupation, and other aspects of her life that are of importance to her. The decision to not treat depression with medication and remain symptomatic and the decision to treat with antidepressant medications may each have short-term implications for infant development. However, it remains encouraging that long-term studies to date on the impact of both depression per se on outcome and antidepressant medications per se on outcome do not suggest significant or major lasting sequelae of either for the child.

Future research designed to assess the relative effects of fetal exposure to depressive symptoms versus antidepressants must include systematic follow-up of women across pregnancy; careful longitudinal quantification of degree, duration, and timing of depression exposure and antidepressant exposure; and standardized, structured assessments of infants and children.

Our review has included only prospective studies in an effort to minimize heterogeneity of data. Our review highlights the paucity of such studies. Even these prospective studies, the best in the field, are heterogeneous with respect to exposure and outcome measurements, providing unclear guidance as to whether untreated depression versus treatment with antidepressants has greater significance for short- and long-term child outcome. Nevertheless, despite limitations of the field thus far, the existing data presented provide a comprehensive review for clinicians in order to help patients and their families make the most informed decisions regarding treatment of major depression during pregnancy. As the field progresses, a better understanding of the factors that confer or attenuate risk for short- and long-term outcomes will hopefully be developed. Mechanisms by which depression and its treatment exert their influence, including translational evaluation of genomic differences between exposed pregnant women and the fetus, should be explored. Further, factors that modulate perinatal and neurobehavioral vulnerability to depression or medication exposure should be studied. Such investigation may elucidate other more subtle but equally significant factors that affect outcome and serve to further refine our understanding of the factors that must be taken into account as women and clinicians work together to make treatment decisions in the management of individual clinical situations.

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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