Management of Major Depression During Pregnancy

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In this report, we describe the case of a woman with recurrent major depression who wished to get pregnant. She was taking a daily antidepressant and sought information on the safety of the medication after conception. This case illustrates 1) the dilemmas that arise in the psychiatric treatment of pregnant and nursing women, 2) the risk-benefit assessments that are involved in the pharmacological treatment of depression during pregnancy and lactation, and 3) approaches to minimize the risk of such treatments.

Case Report

Ms. A was a 36-year-old married woman with a history of recurrent major depression who sought consultation regarding the safety of antidepressant medications during pregnancy. She and her husband hoped to conceive in the near future but were concerned about Ms. A's use of fluoxetine, 20 mg/day. The husband came to the appointment with his wife.

History

Ms. A had a history of three episodes of major depression between ages 24 and 33. She was treated with psychotherapy for her first episode and found it helpful in relieving her symptoms. She continued, however, with recurrent premenstrual dysphoria. After experiencing her second episode of major depression, on the advice of her psychotherapist, she sought psychopharmacological consultation for both the depression and the premenstrual mood symptoms. She started taking fluoxetine, 20 mg/day, which was highly effective in treating both conditions. After a year of treatment, she switched to luteal-phase use of fluoxetine. However, she experienced a relapse of major depression within 8 months. Her depression symptoms included low energy, anhedonia, irritability, poor appetite, insomnia, and low self-esteem. Prompt resumption of fluoxetine, 20 mg/day, produced a full and sustained remission of symptoms, with no recurrence up to the present time. She had no history of suicidality or psychiatric hospitalizations.

Ms. A's medical history was unremarkable. She was a healthy Caucasian woman with regular menstrual cycles and no prior pregnancies. She used a diaphragm for contraception. She was a nonsmoker and did not use illicit drugs. She used alcohol socially.

Course of Treatment

The initial consultation included a detailed review of psychiatric treatment options during pregnancy and a review of the risks and benefits associated with the use of antidepressant medications. Approaches to antidepressant medication management during pregnancy were discussed, including 1) tapering and discontinuing the antidepressant before attempting conception, 2) continuing to take the antidepressant until she had a positive pregnancy test, followed by immediate discontinuation, and 3) continuing to take the antidepressant throughout pregnancy. After listening to her options, Ms. A expressed interest in discontinuing the antidepressant once she had a positive pregnancy test. She was reluctant to stop taking the medication before conception out of concern that premenstrual dysphoric disorder and/or major depression would recur.

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Since the fluoxetine metabolite (norfluoxetine) has an extremely long elimination half-life (7–10 days), the developing fetus would continue to be exposed to this drug for several weeks after medication discontinuation. The plan was therefore made to switch to a shorter-acting medication. Alternative medications were discussed, including side effect profiles and family histories of response. Ms. A mentioned that her sister had responded well to sertraline and that she would like to try this agent. A switch was therefore initiated from fluoxetine, 20 mg/day, to sertraline, 75 mg/day, over the next 10 days.

Ms. A was encouraged to begin individual psychotherapy, and she agreed to this plan. She was given a list of therapists, including several with experience in working with pregnant women and new mothers. She chose a therapist with an eclectic approach that combined psychodynamic and supportive modalities.

At a follow-up visit 6 weeks later, Ms. A remained euthymic and reported no relapse of premenstrual symptoms. She and her husband continued to agree with the plans that were discussed at the first visit and felt that they were ready to stop using contraception.

After 4 months of attempting to conceive, Ms. A called to report that a pregnancy test that morning had given positive results. She discontinued the sertraline as of that day. At her visits 2 and 4 weeks later, she remained euthymic. Follow-up visits were then scheduled monthly. She continued to be well until her sixth month of pregnancy, when she reported that her mood had deteriorated. Ms. A increased her individual therapy to twice-weekly meetings. Two weeks later, she reported that her depression and hopelessness hampered her motivation

for therapy. She added that her appetite was poor and that she had ceased to gain weight. She reported no suicidality but felt apathetic about the pregnancy and had lost her ability to take pleasure in activities she had previously enjoyed, such as attending the theatre or meeting with friends. The potential risks and benefits associated with the prenatal use of antidepressants in the second and third trimesters were reviewed. After considering the information, Ms. A chose to initiate fluoxetine, 20 mg/day. Within 2 weeks, Ms. A felt substantially better, and by 1 month she was euthymic.

At 39½ weeks' gestation, Ms. A delivered a healthy baby girl with 1- and 5-minute APGAR scores of 7 and 9, respectively. She took the same dose of fluoxetine after delivery and, in a phone appointment 2 weeks after the birth, reported feeling tired but generally euthymic. However, at a psychiatric visit 3 weeks after delivery, Ms. A reported difficulty sleeping even when the infant was asleep. She also described a growing apathy toward her parenting responsibilities, which produced a great deal of guilt. Furthermore, she reported a lack of confidence in herself as a mother and wept as she said this. A decision was made to add nortriptyline, 50 mg, at bedtime. This medication was chosen not only to augment fluoxetine but also to help with sleep. At a visit the next week, Ms. A reported that her sleep had improved. Her serum concentration of nortriptyline at that time was 70 ng/ml. Ms. A added that the infant was feeding well and appeared healthy. At a psychiatric visit 6 weeks after delivery, Ms. A reported feeling much better. She held her daughter tenderly and spoke about her with pride. Ms. A continued individual psychotherapy but reduced the frequency to weekly visits.

In visits at 3 and 6 months postpartum, Ms. A remained well. At 6 months postpartum, she weaned her daughter. She also discontinued the antidepressants since she felt she no longer needed them. Furthermore, she believed that the nortriptyline had impeded her efforts to lose the weight she had gained during her pregnancy. Ms. A's menstrual cycles returned at 8 months postpartum. She experienced a recurrence of premenstrual mood changes, and the decision was made to resume taking fluoxetine, which had helped her premenstrual symptoms before her pregnancy. She reported no further premenstrual mood changes in subsequent months of follow-up.

Discussion

This case illustrates the issues that commonly arise in the treatment of depression in women who are pregnant or trying to conceive. The patient wisely sought consultation before pregnancy, thus allowing time for a preconception treatment plan to be reviewed and implemented. Preconception evaluations provide an opportunity to discuss data on exposures to antidepressant medications during pregnancy and lactation, to review a woman's likelihood of a depressive relapse during pregnancy and the postpartum period, and to institute supportive and prophylactic interventions that may reduce the risk of relapse. Ideal management that minimizes risk to both mother and infant remains uncertain since data on the impact of different treatment approaches for pregnant patients are incomplete. Even experts in the field express differing opinions on the optimal treatment of depression in pregnant women (1). The information to date will be reviewed.

The largest amount of information on prenatal antidepressant exposures involves fluoxetine. Neither retrospective nor prospective studies have found a greater risk of miscarriage or major congenital malformations with antidepressant treatment (2–8). Third-trimester use of fluoxetine has been linked with higher rates of perinatal complications (e.g., tachypnea, jitteriness, premature delivery) in some (3, 4), but not all (5–8), studies. A study of 226 prenatal exposures to sertraline, paroxetine, and fluvoxamine (9) found the rates of major malformations and preterm labor were no higher than those of nonexposed comparison subjects. A prospective study that used the Swedish Birth Registry (6) reported 969 cases of prenatal exposure to antidepressants, including citalopram (375 cases), paroxetine (122 cases), sertraline (33 cases), and fluoxetine (16 cases) and reported rates of perinatal complications and congenital malformations comparable to population norms. Among 150 women who took venlafaxine during pregnancy, the incidence of major malformations was no higher than the expected rate of 1%–3% (10).

Prenatal use of tricyclic antidepressants similarly does not appear to increase the risk of congenital anomalies (5, 6), although these medications may produce transient neonatal toxicity or withdrawal symptoms when used near the time of delivery. These symptoms have included lethargy, hypotonia, and anticholinergic effects, such as constipation, tachycardia, and urinary retention (5, 11, 12). Nortriptyline and desipramine are preferable to other tricyclic antidepressants during pregnancy because of their lower likelihood of anticholinergic and hypotensive side effects. Their doses may need to be adjusted over the course of pregnancy since serum concentrations may fall below the therapeutic window (13). A small case series (N= 7) of mirtazapine use in pregnancy (14) found no perinatal complications or congenital malformations in the infants.

A study of 21 prenatal exposures to monoamine oxidase inhibitors (MAOIs) (15) found a relative risk for congenital malformations of 3.4. In contrast, a more recent case report of phenelzine use throughout pregnancy (16) described a healthy outcome for the patient and her infant. Nevertheless, MAOIs are best avoided in pregnant women because of the risk of hypertensive crisis. Additionally, MAOIs contraindicate the use of tocolytic agents (e.g., terbutaline), which may be necessary to prevent premature labor. At present, to our knowledge, no published studies exist on bupropion or nefazodone in pregnancy.

When selecting an antidepressant medication for a pregnant woman, clinicians should be cautious in their use of the Food and Drug Administration (FDA) use-in-pregnancy ratings. These ratings categorize medications into one of five groups on the basis of known risk to the fetus: an "A" rating indicates that controlled studies of the medication show no risk to pregnant women; a "B" rating indicates that no evidence of risk exists to date in humans; a "C" rating is used when risk cannot be ruled out; a "D" rating indicates positive evidence of risk; and an "X" rating

indicates that the medication is contraindicated in pregnancy. A medication carrying an FDA pregnancy category B rating is not necessarily safer to use in pregnancy than a medication with a pregnancy category C labeling. Medications may receive the category B rating in the absence of human data, provided that animal reproduction studies have not demonstrated a fetal risk. A category C medication for which there are human data showing low risk may be preferable to a category B medication for which there are no human studies, as is the case for bupropion. An additional concern regarding fetal exposure to bupropion arises from the medication's seizure-inducing potential.

In contrast to morphological teratogenesis, behavioral teratogenesis has received minimal attention. Behavioral teratogenesis refers to the neurological or behavioral impact that may result in children from prenatal exposure to centrally acting medications. Use of antidepressant medications during pregnancy exposes the child's brain to psychoactive agents at a time of maximal development of the CNS (17, 18). Furthermore, the relatively small proportion of myelin in fetal brains allows medications to accumulate in the CNS (19). Therefore, the safety of antidepressant use in pregnant women cannot be ensured until possible behavioral consequences are studied. Data on the developmental outcomes in children exposed to antidepressants during pregnancy are reassuring but limited. Two prospective studies (8, 20) and one case series (21) have reported developmental outcomes in children prenatally exposed to antidepressants. The first study evaluated 55 children who were prenatally exposed to fluoxetine, 80 children who were prenatally exposed to tricyclic antidepressants, and 84 unexposed children (8) and found no significant differences in global IQ, language development, temperament, mood, distractibility, or behavior in children up to the age of 7. The second study (20), which included 86 infants prenatally exposed to citalopram, fluoxetine, paroxetine, or sertraline, evaluated the children at age 18 months with the Bayley Scales of Infant Development and found scores in the age-appropriate range. In the case series (21), developmental milestones among nine children aged 4 months to 3 years were normal for chronological age after prenatal exposure to tricyclic antidepressants.

While these data are reassuring, the total number of reported exposures remains small. Therefore, discontinuation of an antidepressant before conception is a reasonable approach for women who are stable and, by history, appear likely to remain well for at least several months while not taking the medication. Continuation of the antidepressant until conception is another reasonable option. If the antidepressant is discontinued at the time of a positive pregnancy test (i.e., approximately 12–14 days postconception), the developing embryo will receive minimal medication exposure since the uteroplacental circulation does not form until 10–12 days postconception (22). It is important to keep in mind, however, that short-term discontinuation of an antidepressant may produce withdrawal symptoms (23) and is associated with a risk of relapse to depression over the course of the pregnancy of up to 75% (24, 25). For women like our patient who seek counseling before conception and obtain supportive and prophylactic interventions, it is possible that the relapse risk is lower. Each case must be evaluated on an individual basis by taking into account the number of previous episodes of major depression and the time to relapse after previous attempts at medication discontinuation.

For women with histories of rapid and severe relapse of major depressive episodes after medication discontinuation, the antidepressant may need to be maintained throughout the pregnancy. These recommendations are consistent with the Expert Consensus Guideline Series on Treatment of Depression in Women 2001 (1).

Women who are pregnant or attempting to conceive should be encouraged to initiate psychotherapy if they are not already obtaining it. Interpersonal psychotherapy—a form of therapy that examines role transitions and disputes and deficits in interpersonal interaction—has been evaluated for pregnant women and appears to be effective (26).

The risk-benefit discussion should be recorded in the patient's file along with a statement indicating that the patient understands the information provided and is in agreement with the plan. Whenever possible, the partner and other health care providers should be included in the risk-benefit discussion.

Impact of Depression on Pregnancy

A number of studies have reported an association between maternal anxiety/stress during pregnancy and negative pregnancy outcomes, such as preterm labor and low-birth-weight infants (27–37), even after control for confounding variables such as socioeconomic status, maternal weight gain, and health habits during pregnancy. Fewer investigations have evaluated the impact of maternal major depression on pregnancy outcomes. A recent study of 623 women followed prospectively over pregnancy (38) reported a significant relationship between depression (as measured with the Beck Depression Inventory) and preeclampsia. In another prospective study of 389 women of low socioeconomic class (39), depression during the first trimester of pregnancy was associated with a greater risk of low-birth-weight infants and preterm delivery. In contrast, a prospective study that administered psychiatric interviews to 94 women across pregnancy (40) found no relationship between maternal mood during pregnancy and infant birth weights or gestational ages. This study also found no association between maternal depression during pregnancy and children's cognitive scores on the McCarthy Scales at age 4 years.

In summary, maternal anxiety and stress during pregnancy appear to predict adverse pregnancy outcomes. The impact of maternal major depression on pregnancy outcomes is less clear at this time and requires further investigation.

Risk Factors for Postpartum Relapse

Our patient experienced a recurrence of major depression in the postpartum period, in which she had chosen to remain medication-free while nursing. A woman with a history of major depression, like Ms. A, is at approximately a 25% risk for relapse of depression after childbirth (postpartum depression). Depressive symptoms during pregnancy raise the risk even higher (41). Other risk factors include a conflictual relationship with the baby's father (42), stressful life events (42), low socioeconomic status (43), and frequent health problems in the infant (44).

Postnatal Depression and Children's Outcomes

Ms. A experienced postpartum depression with symptoms including apathy, low energy, guilt, and low self-confidence. Her decision to restart the antidepressant medication helped her significantly and may also have been beneficial for her infant. A substantial literature documents the potential negative impact of maternal postnatal depression on children. Most studies have included women with depression occurring within 3–12 months of delivery rather than the shorter time frame of 4 weeks that DSM-IV defines for "postpartum onset." Therefore, we will use the term "postnatal" rather than "postpartum" when referring to depression occurring within the first year after delivery.

Compared with children of nondepressed mothers, children of mothers who have experienced postnatal depression perform worse on cognitive and behavioral measures (45–51) and exhibit higher rates of insecure attachment (45, 46, 52). Children of mothers who experienced depression in the child's first year of life appear to be at greater risk for adverse cognitive outcomes than children who were older when their mothers experienced depression. Children's exposure to subsequent relapses of maternal depression also appears to increase their risk for poor cognitive outcomes.

Several researchers have evaluated the mechanisms mediating the negative effect of parental depression on children's development and have identified negative parenting behaviors that occur commonly among depressed parents. For example, depressed mothers have been observed to be intrusive or withdrawn and disengaged when interacting with their infants (53, 54) and less sensitively attuned to their infants than healthy women (55). The disturbances in mother-infant interactions observed among depressed mothers were found to highly predict poor infant cognitive outcomes at 18 months (55). A recent study of 2,017 parents of children ages 0–3 years (56) identified parental depressive symptoms as the most consistent predictors of negative parenting behaviors (e.g., yelling, hitting, shaking) after controlling for socioeconomic status, ethnic group, parental years of education, parental age, and parental employment status. For each depressive symptom, the odds that the parent would engage in at least one form of negative interaction rose by 25% for mothers and 43% for fathers (56). These studies indicate that children's exposure to parental depression represents a substantial risk for poor developmental outcomes. Underscoring the importance of intervention, research has found that if maternal depression is prevented, infant problems associated with maternal depression, such as behavioral problems and insecure attachment (57) and decline in IQ (46), can also be prevented.

Treatment of Postpartum Depression

A number of treatment interventions are helpful for postpartum depression and include psychotherapy, support groups, and referrals to self-help and national organizations such as Postpartum Support International (805-967-7636) or Depression After Delivery (800-944-4773). Interpersonal and cognitive behavior therapy are forms of individual psychotherapy that have been found effective for treatment of postpartum depression (58, 59).

Antidepressants are also helpful in relieving postpartum depression (59–61). The choice of antidepressant should take into account whether or not the patient is nursing since antidepressant medications traverse readily into breast milk. To date, the largest literature on the use of antidepressants by nursing women involves the selective serotonin reuptake inhibitors (SSRIs). A study compared 26 nursing infants whose mothers took fluoxetine with 28 nursing infants whose mothers did not take the medication (62) and reported a significantly lower growth rate (although within the normal range) among the fluoxetine-exposed group over the first 6 months of age. The study was retrospective and did not control for the impact of maternal depression on breast-feeding behavior. Also, two case reports (63, 64) attributed uneasy sleep and colic to breast-feeding infants exposed to citalopram and fluoxetine, respectively, through breast milk, with resolution after discontinuation or diminution of breast-feeding. However, several studies totaling more than 210 mother-infant pairs (12, 21, 65–77) observed no adverse effects of SSRI exposure in nursing infants. The majority of these studies involved fluoxetine, sertraline, and paroxetine. These data show that in many cases women can safely continue breast-feeding while taking an antidepressant medication.

A consideration for new mothers who have recently weaned their infants is the potential occurrence of premenstrual mood changes once menstrual cycles resume (78). This is of particular concern for women with histories of premenstrual dysphoric disorder. As in this case, Ms. A's postpartum major depression returned soon after antidepressant discontinuation and remitted with reinstitution of treatment. High relapse rates have been reported for postpartum major depression after treatment discontinuation (79), supporting the need for ongoing treatment for women with this condition.

Summary

Women with histories of major depression may relapse during pregnancy or the postpartum period. Depression during pregnancy can present risks to the mother and fetus, such as inadequate maternal weight gain and, in the extreme, suicidality. After childbirth, maternal depression

may interfere with mother-child bonding and may be detrimental to the infant's development. Psychotherapeutic approaches, including individual psychotherapy, couples counseling, and support groups, can help treat major depression during pregnancy and the postpartum period. If a woman remains depressed despite nonpharmacologic interventions or if her depression is associated with significant morbidity, antidepressant medications should be considered. Given the data on birth outcomes after prenatal exposure to several antidepressant medications and the accumulating data on the use of antidepressant medications by breast-feeding women, the relative benefits of a medication to treat depression in pregnant or nursing women may outweigh the theoretical risk of its use.

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References

1. Altshuler LL, Cohen LS, Moline ML, Kahn DA, Carpenter D, Docherty JP: Treatment of Depression in Women 2001. Postgraduate Medicine: The Expert Consensus Guideline Series, A Special Report, March 2001
2. Addis A, Koren G: Safety of fluoxetine during the first trimester of pregnancy: a meta-analytical review of epidemiological studies. Psychol Med 2000; 30:89–94
3. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL: Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335:1010–1015
4. Cohen LS, Heller VL, Bailey JW, Grush L, Ablon JS, Bouffard SM: Birth outcomes following prenatal exposure to fluoxetine. Biol Psychiatry 2000; 48:996–1000
5. McElhatton PR, Garbis HM, Elefant E, Vial T, Bellemin B, Mastroiacovo P, Arnon J, Rodriguez-Pinilla E, Schaefer C, Pexieder T, Merlob P, Dal Verme S: The outcome of pregnancy in 689 women exposed to therapeutic doses of antidepressants: a collaborative study of the European Network of Teratology Information Services (ENTIS). Reprod Toxicol 1996; 10:285–294
6. Ericson A, Kullen B, Wilholm BE: Delivery outcome after the use of antidepressants in early pregnancy. Eur J Clin Pharmacol 1999; 55:503–508
7. Goldstein DJ: Effects of third trimester fluoxetine exposure on the newborn. J Clin Psychopharmacol 1995; 15:417–420
8. Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JG, Kulin N, Koren G: Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336:258–262
9. Kulin NA, Pastuszak A, Sage SR, Schick-Boschetto B, Spivey G, Feldkamp M, Ormond K, Matsui D, Stein-Schechman AK, Cook L, Brochu J, Rieder M, Koren G: Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. JAMA 1998; 279:609–610
10. Einarson A, Fatoye B, Sarkar M, Lavigne SV, Brochu J, Chambers C, Mastroiacovo P, Addis A, Matsui D, Schuler L, Einarson TR, Koren G: Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. Am J Psychiatry 2001; 158:1728–1730
11. Altshuler LL, Cohen L, Szuba MP, Burt VK, Gitlin M, Mintz J: Pharmacologic management of psychiatric illness during pregnancy: dilemmas and guidelines. Am J Psychiatry 1996; 153: 592–606
12. Wisner KL, Perel JM, Blumer J: Serum sertraline and N-desmethylsertraline levels in breast-feeding mother-infant pairs. Am J Psychiatry 1998; 155:690–692
13. Altshuler LL, Hendrick V: Pregnancy and psychotropic medication: changes in blood levels. J Clin Psychopharmacol 1996; 16: 78–80
14. Saks BR: Mirtazapine: treatment of depression, anxiety, and hyperemesis gravidarum in the pregnant patient: a report of 7 cases. Archives of Women's Ment Health 2001; 4:165–170
15. Heinonen OP, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. Littleton, Mass, Publishing Science Group, 1977
16. Gracious BL, Wisner KL: Phenelzine use throughout pregnancy and the puerperium: case report, review of the literature and management recommendations. Depress Anxiety 1997; 6: 124–128
17. Vitiello B, Jensen PS: Developmental perspectives in pediatric psychopharmacology. Psychopharmacol Bull 1995; 31:75–81
18. Vitiello B: Pediatric psychopharmacology and the interaction between drugs and the developing brain. Can J Psychiatry 1998; 43:582–584
19. Briggs G, Freeman RK, Yaffe SJ (eds): Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 5th ed. Baltimore, Wilkins & Wilkins, 1998
20. Hendrick V: Treatment of postpartum depression: risks to mother and child, in 2001 Annual Meeting Syllabus and Proceedings Summary. Washington, DC, American Psychiatric Association, 2001
21. Misri S, Kim J, Riggs KW, Kostaras X: Paroxetine levels in postpartum depressed women, breast milk, and infant serum. J Clin Psychiatry 2000; 61:828–832
22. Creasy RK, Resnik R: Maternal-Fetal Medicine: Principles and Practice, 3rd ed. Philadelphia, WB Saunders, 1994, pp 96–97
23. Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WR: Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998; 44:77–87
24. Cohen LS, Altshuler LL, Stowe ZN: MGH Prospective Study: depression in pregnancy in women who decrease or discontinue antidepressant medication, in 1999 Annual Meeting Syllabus and Proceedings Summary. Washington, DC, American Psychiatric Association, 1999
25. Einarson A, Selby P, Koren G: Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counseling. J Psychiatry Neurosci 2001; 26:44–48
26. Spinelli MG: Interpersonal psychotherapy for depressed antepartum women: a pilot study. Am J Psychiatry 1997; 154: 1028–1030
27. Rini CK, Dunkel-Schetter C, Wadhwa PD, Sandman CA: Psychological adaptation and birth outcomes: the role of personal resources, stress, and sociocultural context in pregnancy. Health Psychol 1999; 18:333–345
28. Texeira JMA, Fisk NM, Glover V: Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. Br Med J 1999; 318:153–157
29. Sandman CA, Wadhwa PD, Chicz-DeMet A, Dunkel-Schetter C, Porto M: Maternal stress, HPA activity and fetal/infant outcome. Ann NY Acad Sci 1997; 814:266–275
30. Bhagwanani SG, Seagraves K, Dierker LJ, Lax M: Relationship between prenatal anxiety and perinatal outcome in nulliparous women: a prospective study. J Natl Med Assoc 1997; 89: 93–98
31. Copper RL, Goldenberg RL, Das A, Elder N, Swain M, Norman G, Ramsey R, Cotroneo P, Collins BA, Johnson F, Jones P, Meier AM (National Institute of Child Health and Human Development

Maternal-Fetal Medicine Units Network): The Preterm Prediction Study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. Am J Obstet Gynecol 1996; 175:1286–1292
32. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP: Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. J Psychosom Res 1995; 39:563–595
33. Pritchard CW, Teo PV: Preterm birth, low birth weight, and the stressfulness of the household role for pregnant women. Soc Sci Med 1994; 38:89–96
34. Wadhwa PD, Sandman CA, Porto M, Dunkel-Schetter C, Garite TJ: The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. Am J Obstet Gynecol 1993; 169:858–865
35. Hedegaard M, Henriksen TB, Secher NJ, Hatch MC, Sabroe S: Do stressful life events affect duration of gestation and risk of preterm delivery? Epidemiology 1996; 7:339–345
36. Lobel M, Dunkel-Schetter C, Scrimshaw S: Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. Health Psychol 1992; 11:32–40
37. Reeb KG, Graham AV, Zyzanski SJ, Kitson GC: Predicting low birthweight and complicated labor in urban black women: a biopsychosocial perspective. Soc Sci Med 1987; 25:1321–1327
38. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O: Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000; 95:487–490
39. Steer RA, Scholl TO, Hediger ML, Fischer RL: Self-reported depression and negative pregnancy outcomes. J Clin Epidemiol 1992; 45:1093–1099
40. Cogill SR, Caplan HL, Alexandra H, Robson KM, Kumar R: Impact of maternal postnatal depression on cognitive development of young children. Br Med J 1986; 292:1165–1167
41. O'Hara MW: Postpartum Depression: Causes and Consequences. New York, Springer-Verlag, 1995
42. Barnet B, Joffe A, Duggan AK, Wilson MD, Repke JT: Depressive symptoms, stress, and social support in pregnant and postpartum adolescents. Arch Pediatr Adolesc Med 1996; 150:64–69
43. Bergant AM, Heim K, Ulmer H, Illmensee K: Early postnatal depressive mood: associations with obstetric and psychosocial factors. J Psychosom Res 1999; 46:391–394
44. Mandl KD, Tronick EZ, Brennan TA, Alpert HR, Homer CJ: Infant health care use and maternal depression. Arch Pediatr Adolesc Med 1999; 153:808–813
45. Lyons-Ruth K, Zoll D, Connell D, Grunebaum HU: The depressed mother and her one-year-old infant: environment, interaction, attachment, and infant development. New Dir Child Dev 1986; 34:61–82
46. Murray L: The impact of postnatal depression on infant development. J Child Psychol Psychiatry 1992; 33:543–561
47. Cicchetti D, Rogosch FA, Toth SL: The efficacy of toddler-parent psychotherapy for fostering cognitive development in offspring of depressed mothers. J Abnorm Child Psychol 2000; 28: 135–148
48. Murray L, Hipwell A, Hooper R, Stein A, Cooper P: The cognitive development of 5-year-old children of postnatally depressed mothers. J Child Psychol Psychiatry 1996; 37:927–935
49. Hay DF, Kumar R: Interpreting the effects of mothers' postnatal depression on children's intelligence: a critique and reanalysis. Child Psychiatry Hum Dev 1995; 25:165–181
50. Sharp D, Hay DF, Pawlby S, Schmucker G, Allen H, Kumar R: The impact of postnatal depression on boys' intellectual development. J Child Psychol Psychiatry 1995; 36:1315–1336
51. Sinclair D, Murray L: Effects of postnatal depression on children's adjustment to school: teacher's reports. Br J Psychiatry 1998; 172:58–63
52. Teti DM, Gelfand DM, Messinger DS, Isabella R: Maternal depression and the quality of early attachment: an examination of infants, preschoolers, and their mothers. Dev Psychol 1995; 31:364–376
53. Weinberg MK, Tronick EZ: The impact of maternal psychiatric illness on infant development. J Clin Psychiatry 1998; 59(suppl 2):53–61
54. Hart S, Field T, Nearing G: Depressed mothers' neonates improve following the MABI and a Brazelton demonstration. J Pediatr Psychol 1998; 23:251–256
55. Murray L, Fiori-Cowley A, Hooper R, Cooper P: The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. Child Dev 1996; 67:2512–2526
56. Lyons-Ruth K, Wolfe R, Lyubchik A, Steingard R: Depressive symptoms in parents of children under three: sociodemographic predictors, current correlates and associated parenting behaviors, in Child-Rearing in America: Challenges Facing Parents With Young Children. Edited by Halfon N, Schuster M, Taaffe Young K. New York, Cambridge University Press, 2002, pp 217–262
57. Cooper PJ, Murray L: The impact of psychological treatments of postpartum depression on maternal mood and infant development, in Postpartum Depression and Child Development. Edited by Murray L, Cooper PJ. New York, Guilford, 1997, pp 201–220
58. O'Hara MW, Stuart S, Gorman LL, Wenzel A: Efficacy of interpersonal psychotherapy for postpartum depression. Arch Gen Psychiatry 2000; 57:1039–1045
59. Appleby L, Warner R, Whitton A, Faragher B: A controlled study of fluoxetine and cognitive-behavioural counseling in the treatment of postnatal depression. Br Med J 1997; 314:932–936
60. Cohen LS, Viguera AC, Bouffard SM, Nonacs RM, Morabito C, Collins MH, Ablon JS: Venlafaxine in the treatment of postpartum depression. J Clin Psychiatry 2001; 62:592–596
61. Hendrick V, Altshuler L, Strouse T, Grosser S: Postpartum and nonpostpartum depression: differences in presentation and response to pharmacologic treatment. Depress Anxiety 2000; 11:66–72
62. Chambers CD, Anderson PO, Thomas RG, Dick LM, Felix RJ, Johnson KA, Jones KL: Weight gain in infants breastfed by mothers who take fluoxetine. Pediatrics 1999; 104:e61
63. Schmidt K, Olesen OV, Jensen PN: Citalopram and breast-feeding: serum concentration and side effects in the infant. Biol Psychiatry 2000; 47:164–165
64. Lester BM, Cucca J, Andreozzi L, Flanagan P, Oh W: Possible association between fluoxetine hydrochloride and colic in an infant. J Am Acad Child Adoles Psychiatry 1993; 32:1253–1255
65. Kristensen JH, Ilett KF, Hackett LP, Yapp P, Paech M, Begg EJ: Distribution and excretion of fluoxetine and norfluoxetine in human milk. Br J Clin Pharmacol 1999; 48:521–527
66. Yoshida K, Smith B, Craggs M, Kumar RC: Fluoxetine in breastmilk and developmental outcome of breast-fed infants. Br J Psychiatry 1998; 172:175–178
67. Taddio A, Ito S, Koren G: Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. J Clin Pharmacol 1996; 36:42–47
68. Burt VK, Suri R, Altshuler L, Stowe Z, Hendrick VC, Muntean E: The use of psychotropic medications during breast-feeding. Am J Psychiatry 2001; 158:1001–1009
69. Hendrick V, Fukuchi A, Altshuler L, Widawski M, Wertheimer A, Brunhuber MV: Use of sertraline, paroxetine and fluvoxamine by nursing women. Br J Psychiatry 2001; 179:163–166
70. Hendrick V, Stowe ZN, Altshuler LL, Mintz J, Hwang S, Hostetter A, Suri R, Leight K, Fukuchi A: Fluoxetine and norfluoxetine

concentrations in nursing infants and breast milk. Biol Psychiatry 2001; 50:775–782

71. Stowe ZN, Owens MJ, Landry JC, Kilts CD, Ely T, Llewellyn A, Nemeroff CB: Sertraline and desmethylsertraline in human breast milk and nursing infants. Am J Psychiatry 1997; 154: 1255–1260
72. Stowe ZN, Cohen LS, Hostetter A, Ritchie JC, Owens MJ, Nemeroff CB: Paroxetine in human breast milk and nursing infants. Am J Psychiatry 2000; 157:185–189
73. Begg EJ, Duffull SB, Saunders DA, Buttimore RC, Ilett KF, Hackett LP, Yapp P, Wilson DA: Paroxetine in human milk. Br J Clin Pharmacol 1999; 48:142–147
74. Ohman R, Hagg S, Carleborg L, Spigset O: Excretion of paroxetine into breast milk. J Clin Psychiatry 1999; 60:519–523
75. Birnbaum CS, Cohen LS, Bailey JW, Grush LR, Robertson LM, Stowe ZN: Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Pediatrics 1999; 104:e11
76. Piontek CM, Wisner KL, Perel JM, Peindl KS: Serum fluvoxamine levels in breastfed infants. J Clin Psychiatry 2001; 62:111–113
77. Epperson N, Czarkowski KA, Ward-O'Brien D, Weiss E, Gueorguieva R, Jatlow P, Anderson GM: Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. Am J Psychiatry 2001; 158:1631–1637
78. Hendrick V, Altshuler L, Burt VK: Course of psychiatric disorders across the menstrual cycle. Harv Rev Psychiatry 1996; 4:200–207
79. Pearlstein TB, Stone AB: Long-term fluoxetine treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1994; 55:332–335