

**Academy of Breastfeeding Medicine
Annotated Bibliography:
Protocol on Antidepressants and Breastfeeding**

Reference	Content	Level of Evidence*
Background		
Lagoy C, Joshi N, Cragan J, Rasmussen S. Medication Use during Pregnancy and Lactation: An Urgent Call for Public Health Action. Journal of Women's Health 2005; 14(2): 104-109	Describes the commonness of medication usage by women of childbearing age and discusses the lack of good quality research on medication usage during pregnancy and lactation. Describes existing sources of information on the toxic potential of drugs on embryos, fetuses, and neonates, and calls for a central database to monitor adverse outcomes.	III
Burt V, Suri R, Altshuler L, Stowe Z, Hendrick V, Muntean E. The Use of Psychotropic Medicine During Breast-Feeding. Am J Psychiatry 2001; 158(7) 1001-1009	Reviews the data on various psychotropic medications used during lactation. Conclusions based on case reports and small case series only, as no controlled trials were found.	III
Spigset O, Hagg S. Excretion of Psychotropic Drugs into Breast Milk: Pharmacokinetic Overview and Therapeutic Implications. CNS Drugs 1998; 9(2): 111-134	Reviews maternal, fetal, and lactational pharmacokinetics, including cytochrome P450 enzymes. Recommendations are that treatment with tricyclic antidepressants (with the exception of doxepin) is probably not sufficient reason to avoid breastfeeding. Although there is less data on SSRIs, the authors do not recommend avoiding breastfeeding during treatment with this class, with the exception of fluoxetine. More broadly recommends that drugs which are minimally excreted into breast milk or show low levels in infant serum should be preferentially used.	III
Llewellyn A, Stowe Z. Psychotropic Medications in Lactation. J Clin Psychiatry 1998; 59(Suppl 2): 41-52	Reviews literature on psychotropic medication use during lactation. Briefly reviews physiology and pharmacokinetics of lactation and the neonate. Discusses the weaknesses of the literature, including small sample sizes, failure to document portion of breastmilk assayed, limited metabolite assay, limited assay sensitivity, concomitant maternal or infant medications, and medication exposure prenatally. Recommends individual risk/benefit assessment for maternal emotional stability and minimization of infant dose.	III

Metaanalysis		
<p>Weissman A, Levy B, Hartz A, Bentler S, Donohue M, Ellingrod V, Wisner K. Pooled Analysis of Antidepressant Levels in Lactating Mothers, Breast Milk, and Nursing Infants. Am J Psychiatry 2004; 161(6): 1066-1078</p>	<p>Meta-analysis of all case reports, case series, and controlled studies of anti-depressants and breastfeeding from 1966- July 2002, including 36 unpublished cases. Infants with recent prenatal exposure and symptomatic infants were analyzed separately. Breast milk drug levels were averaged if more than one level was reported. Only one measurement per subject was included if multiple were available. Infant serum levels reported as undetectable were recorded as 0, and levels reported as not quantifiable were recorded as 0.1 ng/ml lower than the limit of quantification. Weighted sums of metabolites were also included in analysis, but did not result in any significant changes, except with venlafaxine, where the average infant serum level increased from 0.0 to 0.06 ng/ml. Drugs were detected in breast milk for all anti-depressants studied. Nortriptyline, paroxetine, and sertraline usually produced undetectable infant serum levels. Fluoxetine resulted in 22% of infants having serum drug levels greater than 10% of maternal level. Citalopram produced elevated serum drug levels in 17% of infants, although there is less data available. Other anti-depressants had too few subjects reported for significant conclusions to be made.</p>	<p>II-2</p>
Multiple Drugs		
<p>Hendrick V, Smith L, Hwang S, Altshuler L, Haynes D. Weight Gain in Breastfed Infants of Mothers Taking Antidepressant Medications. J Clin Psychiatry 2003; 64(4): 410-412</p>	<p>Prospective longitudinal cohort study of 78 breastfeeding women treated with antidepressants and their infants. Medications included citalopram (n=3), fluoxetine (n=29), fluvoxamine (n=3), paroxetine (n=15), sertraline (n=25), and venlafaxine (n=3). At 6 months of age, infants weights were not statistically different from normative populations of breastfed infants. However, infants of mothers who relapsed to depressive episodes greater than 2 months had significantly less weight gain than infants whose mothers relapsed to shorter depressive episodes or remained euthymic.</p>	<p>II-3</p>
<p>Birnbaum C, Cohen L, Bailey J, Grush L, Robertson L, Stowe Z. Serum Concentrations of Antidepressants and Benzodiazepines in Nursing Infants: A Case Series. Pediatrics 1999; 104(1): e11-21</p>	<p>Study of 35 nursing infants whose mothers were treated with psychotropic medications. Medications included clomipramine (n=1), desipramine (n=4), imipramine (n=2), nortriptyline (n=4), fluoxetine (n=12), paroxetine (n=2), sertraline (n=3), clonazepam (n=11), trifluoperazine (n=1), and valproic acid (n=2), with 6 women taking multiple medications. Serum drug concentrations were below the limit of detection (5-50 ng/ml) in 26/35 infants. The 9 infants with detectable serum concentrations had all been exposed to medications during the third trimester of pregnancy; 7/9 were infants of mothers treated with fluoxetine. No adverse events reported.</p>	<p>II-3</p>

<p>Berle J, Steen V, Aamo T, Breilid H, Zahlsen K, Spigset O. Breastfeeding During Maternal Antidepressant Treatment With Serotonin Reuptake Inhibitors: Infant exposure, Clinical Symptoms, and Cytochrome P450 Genotypes. J Clin Psychiatry 2004 65(9): 1228-1234</p>	<p>Controlled study of 25 mothers treated with citalopram (n=9), sertraline (n=6), venlafaxine (n=3), paroxetine (n=6), and fluoxetine (n=1) for depression while breastfeeding and their 26 infants. After at least 14 days of treatment to reach steady state, 10 breast milk samples taken over 24 hours and one venous serum sample each from the mother and infant were analyzed for drug and metabolite concentrations. The serum samples were also analyzed for CP450 genotype. Infant symptoms were also assessed using an infant symptom questionnaire designed by the authors. Sixty-eight control mothers who were breastfeeding but not taking antidepressants, also completed the questionnaire. Sertraline and paroxetine were not detected in any infants. Citalopram was detected at low levels in 6/10 infants. Venlafaxine was detected in 3/3 infants. Two poor metabolizer mothers and one infant were identified, but both infants had undetectable or low serum anti-depressant levels.</p>	<p>II-3</p>
<p>Tricyclics</p>		
<p>Yoshida K, Smith B, Craggs M, Kumar R. Investigation of pharma-cokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk. Journal of Affective Disorders 1997; 43:225-237</p>	<p>Controlled prospective study of 10 mother-infant pairs breastfeeding while being treated with imipramine (n=4), amitriptyline (n=2), clomipramine (n=2), and dothiepin (n=2) and 15 bottle-fed infants of depressed mothers as controls. One mother in the study group was also treated with haloperidol. Drug concentration was measured in maternal breast milk, plasma, and urine, and in infant plasma and urine by gas chromatography and enzyme immunoassay. Infant medication dose was found to be about 1% of maternal dose/kg, with higher concentrations of the drugs present in hind milk. Medications were detected in 6/6 infants' plasma (0.6-7.5 ng/ml), and 9/10 infants' urine. No adverse effects reported. Infant development was grossly normal in both control and study groups as measured by the Bayley Scale of Infant Development and the Amiel-Tison neurological assessment up to 30 months of age.</p>	<p>II-3</p>
<p>Wisner K, Perel J. Serum Nortriptyline Levels in nursing Mothers and Their Infants. <i>Am J Psych</i> 1991; 148(9):1234-1236 AND Nortriptyline Treatment of Breast-feeding Women. Am J Psychiatry 1996; 153(2): 295</p>	<p>Twelve mother-infant pairs breastfeeding while treated either prophylactically or for diagnosed postpartum depression with nortriptyline 75-110 mg daily. Levels obtained after at least 7 days on medication. No infants had detectable serum nortriptyline levels, while 2 infants had low detectable levels of 10-hydroxymetabolite.</p>	<p>III</p>

Selective Serotonin Reuptake Inhibitors: Paroxetine, Fluoxetine, Sertraline, Citalopram		
Misri S, Kim J, Riggs K, Kostaras X. Paroxetine Levels in Postpartums Depressed Women, Breast Milk, and Infant Serum. J Clin Psychiatry 2000; 61(11): 828-832	Uncontrolled case series of 24 mothers taking paroxetine 10 mg (n=12), 20 mg (n=10), or 40 mg (n=3) daily while breastfeeding. After 30 days to achieve steady state, venous blood samples were collected from mother and infant 6 hours after dose, as well as a breastmilk sample. These were analyzed with a limit of detection 0.1 ng/mL. Detectable levels of paroxetine were found in 24/25 samples of breast milk, approximately 1.1% of maternal dose. Paroxetine was not detected in any infant serum sample, and no adverse effects were reported.	III
Stowe Z, Cohen L, Hostetter A, Ritchie J, Owens M, Nemeroff C. Paroxetine in Human Breast Milk and Nursing Infants. Am J Psychiatry 2000; 157(2): 185-189	Uncontrolled prospective study of maternal breast milk, serum, and infant serum in 16 breast-feeding mother-infant pairs being treated with paroxetine 10-50 mg daily. Samples were obtained after a minimum of 10 days of treatment. Breast milk samples were obtained either by collecting the fore milk over a 24 hour period, or several samples from one feeding were collected. Paroxetine was detected in all breast milk samples (2-101 ng/ml), with higher concentrations in hind milk. Milk to plasma ratio varied from 0.056 to 1.3, depending on aliquot analyzed. Paroxetine was not detected in any of the infant serum samples with 2.0 ng/ml sensitivity. No adverse events reported.	III
Merlob P, Stahl B, Sulkes J. Paroxetine during breast-feeding: infant weight gain and maternal adherence to counsel. Eur J Pediatr 2004; 163: 135-139	Controlled prospective cohort study of 27 mothers who took paroxetine for major depression during lactation and sought information about this from the Beilinson Teratology Informations Service. Treatment time varied from less than one month (n=5), 1-3 months (n=3), 4-9 months (n=9), one year (n=7), or more (n=2). Control groups consisted of mothers treated with paroxetine who did not breastfeed, and mothers who breastfed but did not take medications. Mothers completed detailed outcome questionnaires 3-12 months after the birth. Additional information was obtained from pediatric and nurse records. Irritability in one infant was the only reported adverse effect. Infants had developmental milestones and 6 and 12 month weight gain similar to both control groups and the general population. Infants in the study group gained less weight than breastfed infants whose mothers did not take medications.	II-3

<p>Kristensen J, Ilett K, Hackett L, Yapp P, Paech M, Begg E. Distribution and excretion of fluoxetine and norfluoxetine in human milk. Br J Clin Pharmacol 1999; 48:521-527</p>	<p>Uncontrolled study of 14 breastfeeding mothers treated with fluoxetine and their infants. Fluoxetine and norfluoxetine concentrations were measured in plasma and milk over 8 hours in 4 mothers and single point data collection in 10. Blood samples were taken from 9 infants. Mean milk to plasma ratio was 0.74 for fluoxetine and 0.62 for norfluoxetine. Total infant exposure was calculated to be 6.81% of weight adjusted maternal dose. Fluoxetine was detected in plasma of 5/9 infants, and norfluoxetine in 7/9, with higher concentrations in younger infants. Two infants were described by their mothers as colicky, and one of these was also "hyperactive." Two infants whose mothers had used fluoxetine during the third trimester had been referred for study due to "withdrawl" symptoms postnatally (uncontrollable crying, irritability, and poor feeding).</p>	<p>III</p>
<p>Hendrick V, Stowe Z, Althshuler L, 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</p>	<p>Uncontrolled prospective study of 19 nursing mothers treated with fluoxetine 10-60 mg daily, 17 of whom were also treated during pregnancy, and their 20 infants. Mothers were treated at least 6 weeks before collection of serum, breastmilk, and infant serum. Nine subjects collected all breast milk for one 24 hour period. Fluoxetine was detectable in the serum of 6/20 infants, and norfluoxetine in 17/20, with a limit of detection 2.0 ng/ml. Peak breast milk levels were detected 8 hours after medication dose. Lower serum concentrations were found in infants whose mothers were taking less than 30 mg daily. No adverse effects reported.</p>	<p>III</p>
<p>Suri R, Stowe Z, Hendrick V, Hostetter A, Widawski M, Altshuler L. Estimates of Nursing Infant Daily Dose of Fluoxetine through Breast Milk. Biol Psychiatry 2002; 52:446-451</p>	<p>Uncontrolled study of 10 breastfeeding mother infant pairs. Breast milk samples were analyzed for fluoxetine and infant dose was calculated in 3 different ways: average 24-hour breast milk concentration, maximum and minimum breast milk 24-hour concentration, and gradient of excretion of medication into breastmilk. Gradient of excretion correlated best with observed infant serum levels of fluoxetine.</p>	<p>III</p>
<p>Epperson C, Jatlow P, Czarkowski, K, Anderson, G. Maternal Fluoxetine Treatment in the Postpartum Period: Effects on Platelet Serotonin and Plasma Drug Levels in Breastfeeding Mother-Infant Pairs. Pediatrics 2003; 112(5): 425-429</p>	<p>Uncontrolled prospective study of platelet serotonin and plasma fluoxetine and norfluoxetine in 11 breastfeeding mother-infant pairs before and after 4-12 weeks of daily maternal fluoxetine treatment at 20 mg (n=5), 30 mg (n=4), or 40 mg (n=2) for postpartum depression. Ten of the eleven infants had minimal changes in platelet serotonin level pre- and post-exposure, while the one infant who had a detectable plasma fluoxetine had a 40% decrease in platelet serotonin. Four months later, plasma drug levels were undetectable and plasma serotonin was no longer reduced; the mother breastfed less and supplemented. No adverse effects reported.</p>	<p>III</p>

<p>Heikkinen T, Ekblad U, Palo P, Laine K. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. Clinical Pharmacology & Therapeutics 2003; 73(4): 330-337</p>	<p>Study of 11 mothers treated with fluoxetine (20-40 mg daily) during pregnancy and lactation for depression (n=5) or panic disorder (n=6), controlled for obstetric variables. Trough plasma samples were collected during pregnancy, delivery, and two months after delivery in the study group. Breastmilk samples were collected on postpartum day 4, at 2 weeks, and at 2 months. At 2 weeks, trough fluoxetine levels were under the limits of detection in 8 of 10 infants (10 nmol/ml), while norfluoxetine was detectable in all infants (53-312 nmol/ml). At 2 months, 0/8 infants had detectable fluoxetine, though 6/8 still had low levels of norfluoxetine detected. Estimated infant exposure to fluoxetine through breastmilk was 2.4% of maternal dose at 2 weeks and 3.8% at 2 months. One infant in the treatment group had polyhydramnios at 37 weeks gestation of unknown etiology, and the treatment group had lower mean 15 minute Apgar scores than the control group. Both groups had normal growth and weight gain and normal neurological development at 12 months of age.</p>	<p>II-3</p>
<p>Chambers C, Anderson P, Thomas R, Dick L, Felix R, Johnson K, Jones K. Weight Gain in Infants Breastfed by Mothers Who Take Fluoxetine. Pediatrics 1999; 104(5): e61</p>	<p>Controlled retrospective cohort study of 26 infants whose mothers had taken fluoxetine 20 mg daily during pregnancy and breastfed at least two weeks postpartum while continuing treatment compared to 38 infants whose mothers had been treated with fluoxetine during pregnancy, but were not taking the medication while breastfeeding. During breastfeeding, 21/26 mothers took 20 mg q day fluoxetine, 1/26 took 30 mg q day, 2/26 alternated between 20 mg and 40 mg, and 2 took 40 mg q day. Infants in the treatment group gained significantly less weight than controls (1.2 SD) between 2 weeks and 6 months of age. No adverse events were reported. Multiple confounding factors.</p>	<p>II-3</p>
<p>Heikkinen T, Ekblad U, Kero P, Ekblad S, Laine K. Citalopram in Pregnancy and Lactation. Clinical Pharmacology & Therapeutics 2002; 72(2); 184-191</p>	<p>Prospective study of 11 mothers treated with citalopram 20-40 mg daily during lactation for depression (n=6) or panic disorder (n=5), controlled for obstetric characteristics. Nine were also treated during pregnancy. Trough venous blood samples were collected from the mother three times during pregnancy, and from the mother and infant at delivery and postpartum days 2 and 4. Breastmilk samples were obtained on postpartum day 4, at 2 weeks, and at 2 months. Mean estimated infant dose of citalopram and metabolites was 0.3% and 0.2% of maternal dose at 2 weeks and 2 months, respectively. Infant weight and neurological development were followed up to one year and classified as normal in all infants.</p>	<p>II-3</p>

<p>Lee A, Woo J, Ito S. Frequency of infant adverse events that are associated with citalopram use during breast-feeding. Am J Obstet Gynecol 2004; 190(1):218-221</p>	<p>Prospective, observational cohort study of 31 mother-infant pairs who contacted a teratogen/toxicant counseling service and elected to be treated with citalopram 10-60 mg daily while breastfeeding. Controls were 12 depressed women who elected not to undergo citalopram therapy (7 received another SSRI) and their infants, and maternal age and parity matched controls not taking medications. Adverse events included 1 case of colic, 1 of decreased feeding, and 1 of irritability/restlessness in the study group, no adverse events in the second group, and 1 case of "gassiness" in the matched controls. None of these required medical treatment, although the mother of the infant with irritability/restlessness discontinued breastfeeding, which improved the symptoms. The number of adverse events reported did not differ significantly between groups. No maternal adverse events reported.</p>	<p>II-3</p>
<p>Dodd S, Stocky A, Buist A, Burrows G, Maguire K, Norman T. Sertraline in Paired Blood Plasma and Breast-Milk Samples from Nursing Mothers. <i>Human Psychopharmacol. Clin. Exp.</i> 2000; 15:261-264</p>	<p>Prospective study of 10 breastfeeding mothers treated for depression (DSM-3R) with sertraline 50-150 mg daily. One blood sample and one breast milk sample were obtained after at least 2 weeks of treatment; two infant plasma samples were also obtained. Sertraline was not detected in either infant sample, with an estimated limit of detection of 10 ng/ml. The infant dose was calculated to be 2-3% of maternal dose. Milk to plasma ratio of sertraline was calculated as approximately 2. Metabolites were not measured.</p>	<p>III</p>
<p>Wisner K, Perel J, Blumer J. Serum Sertraline and N-Desmethylsertraline Levels in Breast-Feeding Mother-Infant Pairs. Am J Psychiatry 1998; 155(5):690-692</p>	<p>Prospective study of 9 mother-infant pairs being treated for major depression (DSM-IV), 3 of whom had co-morbid OCD, with sertraline 50-200 mg daily while breastfeeding. Levels of sertraline were less than 2 ng/ml in 7/9 infants, 3 ng/ml in 1/9, and high in another, which the authors believed to be a spurious finding. N-desmethylsertraline was not quantifiable in 2/9 infants, less than 6 ng/mL in 5/9, while 1 infant had a level of 24 ng/mL despite no detectable sertraline. No developmental or health effects reported by parents or pediatricians.</p>	<p>III</p>
<p>Epperson N, Czarkowski K, Ward-O'Brien D, Weiss E, Gueorguieva R, Jatlow, P, Anderson G. Maternal Sertraline Treatment and Serotonin Transport in Breast-Feeding Mother-Infant Pairs. Am J Psychiatry 2001; 158(10): 1631-1637</p>	<p>Prospective, uncontrolled cohort study of 14 mothers treated with sertraline 25 mg daily (n=1) or 50 mg daily (n=13) and their breastfeeding infants. Maternal sertraline dose was increased as clinically indicated, with mothers eventually receiving daily doses at 25 (n=1), 50 (n=6), 100 (n=5), 150 (n=1), or 200 mg (n=1). Platelet serotonin levels were measured in mothers and infants before and 6-16 weeks after initiation of therapy, depending on maternal increased dose. Sertraline and desmethylsertraline levels were less than 2.5 and 5.0 ng/ml respectively in the 11 infants tested. Mean infant platelet 5HT concentration were not significantly different pre- and post-exposure.</p>	<p>III</p>

<p>Stowe Z, Owens M, Landry J, Kilts C, Ely T, Llewellyn A, Nemeroff C. Sertraline and Desmethylsertraline in Human Breast Milk and Nursing Infants. Am J Psychiatry 1997; 154(9): 1255-1260</p>	<p>Uncontrolled prospective study of 12 women treated with sertraline for depression, while breastfeeding and 11 of their infants. Three mother-infant pairs were also treated while pregnant. Maternal serum, breastmilk, and infant serum samples were analyzed for sertraline and desmethylsertraline at steady state. The highest concentration of sertraline in was found in hind milk 7-10 hours after dose, but present in all breastmilk samples. Milk to plasma ratio was 2.3 for sertraline and 1.4 for desmethylsertraline. Sertraline was detected in the serum of 3/11 infants, and desmethylsertraline in 6/11, minimum level of detection 5 ng/ml. No adverse effects reported.</p>	<p>III</p>
<p>Epperson C, Anderson G, McDougle C. Sertraline and Breastfeeding. N Engl J Med 1997; 336(16): 1189-1190</p>	<p>Uncontrolled study of 4 mothers treated with sertraline for postpartum depression and their infants. Mother took 50 mg daily for 12 weeks or 100 mg daily for 9 weeks. Pre- and post- treatment platelet serotonin levels were measured in mothers and infants, since platelet 5HT transporters are identical to neural transporters. Although maternal platelet 5HT decreased, infant platelet 5HT did not change significantly. Infant sertraline and desmethylsertraline serum levels were less than 2.5 ng/mL and 5 ng/mL respectively.</p>	<p>III</p>
<p>Others: Bupropion, St. John's Wort</p>		
<p>Haas J, Kaplan C, Barenboim D, Jacob P, Benowitz N. Bupropion in breast milk: an exposure for potential treatment to prevent postpartum tobacco use. Tob Control 2004; 13:52-56</p>	<p>Uncontrolled cohort study. Ten postpartum women given bupropion 150 mg daily for 3 days, then 300 mg daily for 4 days while pumping and discarding breast milk. Breastmilk, plasma, saliva, and urine were analyzed for bupropion and metabolites. The average amount in breast milk was 6.75 mcg/kg/day, making the potential infant dose of bupropion and metabolites 0.2% of weight normalized maternal dose. Urine bupropion levels correlated with breastmilk levels.</p>	<p>III</p>
<p>Lee A, Minhas R, Matsuda N, Lam M, Ito S. The Safety of St. John's Wort (<i>Hypericum perforatum</i>) During Breastfeeding. J Clin Psychiatry 2003; 64(8): 966-968</p>	<p>Prospective, observational, controlled cohort study of breastfeeding mothers who inquired about the safety of St. John's wort during breastfeeding at a teratogen/toxicant counseling service, and their infants. The study group consisted of 33 mothers who elected to take St. John's Wort (225-1250 mg daily) while breastfeeding, 100 mothers who elected not to take the medication (disease matched control), and 33 age and parity matched women as a second control. More women in the study group were also taking a prescription anti-depressant than the other two groups. No maternal adverse effects in any group, no significant differences reported in milk production. In study group, 2 cases of "colic", 2 of "drowsiness", and 1 of "lethargy," none requiring medical treatment, and 2 of these infants were also exposed to anti-depressants. This was significantly different than the other groups, in which only 1 case of colic</p>	<p>II-3</p>

reported in each. No differences in weight gain.
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Summary

Approximately 13% of women will experience postpartum depression. Postpartum depression can have serious consequences for both mothers and children. An unknown proportion of women who experience postpartum depression require antidepressant medication to adequately treat their symptoms. Other populations of women who may require postpartum antidepressant medication required antidepressants throughout pregnancy and/or require prophylactic medication to prevent a postpartum episode. For all of these women, three choices exist: 1) breastfeed while taking medication and expose their infant to medication; 2) discontinue medication to breastfeed without risk of medication exposure but with the risk of a clinically significant depression; or 3) continue medication and discontinue nursing. To make an informed decision, mothers and providers, need to have information that reflects sufficient breadth and depth of data regarding individual antidepressant medications. Despite many publications of antidepressants and breastfeeding, the scientific literature lacks both the breadth and depth for individual medications. Multiple reviews of the literature broadly suggest tricyclic and serotonin reuptake inhibitors are relatively safe and all recommend individual risk-benefit assessments.

The literature suffers from a lack of any randomized clinical trials for any class of antidepressant. The majority of studies are case reports or case series and most have small sample sizes. Those studies that report larger samples (N>25) primarily report a variety of medications. Only five controlled studies (1 retrospective, 4 prospective) were found which use a variety of controls – some control for depression while others do not. None of the studies sufficiently control for level of depression. In addition, some case reports are confounded by in-utero exposure due to the timing of the infant assessment. The reports are also limited by the range of infant ages, inconsistencies in the timing of when samples were obtained, lack of information about the amount of medication in foremilk vs. hindmilk and no information about infant consumption as average breastmilk volumes are not provided. The majority of studies provide information about the amount of medication detected in breast milk and maternal serum. Some studies also provide information about infant serum levels of medication. Few studies report infant behavioral outcomes. The majority of studies that do report infant outcomes report general information such as “no adverse events” but do not describe how adverse events were assessed. When infant outcomes were more fully assessed, the primary outcomes reported are weight and behavior/neurological outcomes. One study did use specific infant assessments.

In a recent meta-analysis, all antidepressants were detected in breastmilk. Infant serum levels of nortriptyline, paroxetine and sertraline were undetectable in most cases. Few adverse outcomes were reported. Fluoxetine reached > 10% of maternal serum levels in 22% of the cases and citalopram had elevated levels in 17% of cases. Insufficient cases for other antidepressants were available to make conclusions.