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Original Article

Discontinuation Syndrome in Newborns Whose Mothers Took Antidepressants While Pregnant or Breastfeeding

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Abstract

Objective: This study compared mothers' report of symptoms of discontinuation syndrome in infants exposed to antidepressants both in utero and during lactation to infants who were exposed only during lactation.
Study Design: This is a convenience sample of 930 women breastfeeding women who answered an online questionnaire about antidepressant use while pregnant and breastfeeding. All 930 women had taken antidepressants while breastfeeding, and 527 had also taken antidepressants during pregnancy. There were no participants in the present study who had taken antidepressants only during pregnancy. The questionnaire was posted on the first author's Medications and Breastfeeding Forum. There was no advertising of this study, nor were efforts made to recruit women into this study beyond posting a notice on the website. The questionnaire included a list of symptoms that mothers may have observed in their infants during the newborn period, as well as demographic questions, and questions about antidepressant use during pregnancy and lactation.
Results: The majority of women reported that their infants never experienced the symptoms of discontinuation syndrome. Twenty-five percent reported infant irritability. A smaller percentage reported inconsolable crying (17%), low body temperature (14%), and significant problems with eating and sleeping (15%). Logistic regression revealed that mothers who took antidepressants while pregnant and then during breastfeeding were two to eight times more likely to report symptoms of discontinuation syndrome than women who took them only while breastfeeding. Discontinuation symptoms were more likely to occur in infants whose mothers took medications with shorter half-lives.
Conclusions: Discontinuation syndrome does occur in a small percentage of infants exposed to antidepressants in utero. Mothers reported a higher frequency of discontinuation syndrome after in utero exposure followed by breastfeeding than when infants were exposed to antidepressants only during lactation.

Introduction

When neonates have been exposed to antidepressants in utero, some exhibit withdrawal symptoms, or discontinuation syndrome, for the first 24–48 hours after birth.[1] Discontinuation syndrome is characterized by poor adaptation, jitteriness, irritability, and poor gaze control after gestational exposure to selective serotonin reuptake inhibitors (SSRIs). Some symptoms observed in neonates could be due to the immaturity of the newborns' central nervous system, but they could be due to characteristics of the medications themselves.[2] Medications that enter the central nervous system, in particular SSRIs, transfer readily into the fetal circulation at levels comparable to maternal plasma.[2] Discontinuation syndrome has been reported for fluoxetine, sertraline and paroxetine, but not for all infants.[3,4] Results from previous studies vary with regard to frequency of symptoms of discontinuation syndrome.

For example, in a prospective study of infants exposed to fluoxetine, sertraline, or paroxetine ($n = 46$) in the second and third trimester, all but one of the infants were reported healthy and full term at birth.[5] Thirty-nine percent of the infants exposed to both an SSRI and clonazepam, and 25% of the infants exposed to an SSRI alone, had discontinuation symptoms. The most common symptoms were mild respiratory distress (transient tachypnea of the neonate) and, in some rare cases, hypotonia. These effects were especially likely when paroxetine was combined with clonazepam as clonazepam appeared to change metabolism of paroxetine. When these infants were assessed at 2 and 8 months on the Bayley Scales of Infant Development, there were no significant differences between the exposed and nonexposed groups.

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Boucher et al.[2] compared chart and maternal reports of 146 infants, 73 of whom were exposed prenatally to SSRIs. They found that high-arousal symptoms, such as insomnia, irritability, restlessness, increased tonus, hyperactive reflexes, and tremors, were present in 33 exposed neonates compared with four nonexposed infants. Symptoms of lower arousal, such as decreased reactivity, decreased tonus, and decreased reflexes, were also more common in the exposed versus nonexposed infants (26% vs. 5%).

In a large population study of prenatal exposures to SSRIs in British Columbia ($n = 119{,}547$),[6] the percentage of infants exposed to SSRIs ranged from 2.3% to 5% over the 39-month recruitment period. The rates of complications for SSRI-exposed (vs. nonexposed) infants were as follows: 13.9% for neonatal respiratory distress (vs. 7.8%), 9.4% for jaundice (vs. 7.5%), and 3.9% for feeding problems (vs. 2.4%). The authors concluded that exposure to prenatal SSRIs was associated with increased risk of low birth weight and respiratory distress, even after controlling for maternal depression severity.

Results from these previous studies indicate that studies with smaller sample sizes often have a higher percentage of babies who exhibit these symptoms compared to studies with large samples. Percentages of infants with symptoms range from 4% to 45%, making it difficult to estimate the prevalence of these symptoms. Previous studies have also compared infants exposed to antidepressants in utero to those not exposed. None of these studies specifically compared the effects of prenatal exposure to exposure via breastfeeding. This question has important clinical implications as others have questioned whether SSRI exposure via breastfeeding alone is safe.[7] Do infants exposed to antidepressants via breastfeeding show symptoms similar to those exposed prenatally? Or is prenatal exposure necessary to create a sufficient "loading dose," which causes later withdrawal symptoms in neonates?

The present study examines mothers' report of symptoms in a large sample of breastfeeding women who took antidepressants while pregnant and breastfeeding. The first purpose of the study is to describe antidepressant use during pregnancy and breastfeeding. The second is to compare reported symptoms in infants whose mothers took antidepressants while pregnant and then breastfeeding with infants whose mothers took antidepressants only while breastfeeding. Because of the potential for dependence following prenatal exposure, we hypothesize that a higher percentage of infants who were exposed prenatally to these medications prenatally will exhibit symptoms than those exposed only during breastfeeding.

Subjects and Methods

Participants

A total of 1,884 women participated in the study. Data derived only from the 930 women who took antidepressants while pregnant or breastfeeding were included in the analyses. Data were collected via an online survey conducted between July 26, 2005 and October 27, 2006. The mean age was 32.35 years, with 55% of the mothers between 30 and 40 years of age and 37.83% between 20 and 30 years of age. The women were well educated: 32.8% completed college, and an additional 35.8% had postgraduate education. Twenty-two percent had several years of college, 8.5% were high school graduates, and 1.1% had not completed high school. Ninety-six percent lived with someone other than their children, and 32.5% had an immediate family member with a history of depression or anxiety.

Survey

The survey was developed as part of a broader research study on use of antidepressants in breastfeeding women. There were 53 close-ended items. Mothers were provided with a list of symptoms, including jitteriness, vomiting, irritability, low body temperature, inconsolable crying, shivering, stiffness, moaning, significant eating and sleeping problems, and convulsion, and asked to identify whether they had observed these symptoms in their babies. The individual items were based on symptoms reported in the literature and symptoms that were known to be relevant based on the clinical experiences of the authors. The survey was approved by the Texas Tech University Health Sciences Center (Amarillo, TX) Institutional Review Board before being listed on the website.

Recruitment

The survey was published online as part of the first author's web forum on medications and breastfeeding. Mothers were asked to participate on this website. They were eligible to participate if they were over the age of 18 and had breastfed a baby. A brief description of the survey was listed on the first page. No other method was used by the researchers to recruit mothers for the study, but some participants posted the link for the study on listservs, such as LACTNET.

Measurement

All questions on the questionnaire were close-ended, with mothers being asked to select their answers from the list provided. Mothers were asked two questions about whether they took an antidepressant while pregnant or breastfeeding and were then provided a list of common 13 antidepressants. They could check all that applied. They were asked if they noticed any of the following symptoms during the first week after delivery: jitteriness, vomiting, irritability, low body temperature, inconsolable crying, shivering, stiffness, moaning, significant eating and sleeping problems, and convulsion.

The questions regarding mothers' potential risk factors for depression included maternal age, maternal education level, whether she was living with someone, her family history of depression, and the severity of her most recent depression episode. Each of these was included in the analyses described below.

Analytic strategy

Logistic regression was used to analyze the odds of infants experiencing each of the nine discontinuation symptoms when mothers took antidepressant during pregnancy versus antidepressant use only during breastfeeding. These symptoms include jitteriness, vomiting, irritability, low body temperature, inconsolable crying, shivering, stiffness, moaning, significant eating and sleeping problems, and convulsion. Because of the rarity of convulsion, convergence was not reached. We controlled for maternal age, maternal education, maternal family history of depression, and severity of depression. These variables are shown to influence mothers' depression, and this model controlled for them.

Table 1. Medications Taken While Pregnant

Medication name	Percentage (number) of women who took antidepressants while	
	Pregnant	*Breastfeeding*
Sertraline (Zoloft)	36.2% (188)	50.9% (405)
Fluoxetine (Prozac)	22.5% (117)	14.5% (115)
Paroxetine (Paxil)	12.1% (63)	12.2% (97)
Bupropion (Wellbutrin)	10.8% (56)	6.4% (51)
Citalopram (Celexa)	7.6% (39)	7.2% (57)
Escitalopram (Lexapro)	6% (31)	4.7% (37)
Venlafaxine (Effexor)	4% (21)	3.4% (27)
Nefazodone (Serzone)	0.4% (2)	0.1% (1)
Desipramine	0.2% (1)	0%
Trazodone	0.2% (1)	0%
St. John's wort	0.2% (1)	0.4% (3)
Mirtazapine	0%	0.1% (1)
Amitriptyline	0%	0.1% (1)
Total	520	795

Zoloft®, Pfizer (New York, NY); Prozac®, Eli Lilly and Co. (Indianapolis, IN); Paxil®, GlaxoSmithKline (London, UK); Wellbutrin®, GlaxoSmithKline; Celexa®, Forest Pharmaceuticals (New York); Lexapro®, Forest Pharmaceuticals; Effexor®, Pfizer; Serzone®, Bristol-Myers Squibb (New York).

To further understand the impact of antidepressants of different half-lives and the trimester the mothers started taking an antidepressant, we conducted another series of logistic regression based on a subsample of mothers who took an antidepressant while pregnant and breastfeeding. Paroxetine was classified as an antidepressant with a short half-life, whereas fluoxetine and sertraline were classified as antidepressants with long half-lives. Other antidepressants were classified as antidepressants with mid-range half-lives.

Results

Antidepressant use and self-reported depression

Nine hundred thirty women breastfed while taking antidepressants, and 527 (27.9%) women had also taken an antidepressant while pregnant. In terms of number of days of antidepressant use, 1% took them less than 30 days, 2.5% took them for 31–90 days, 4.95% took them for 91–182 days, and 91% took them for 183 days or more.

Table 1 lists the antidepressants taken during pregnancy. Seventy-three percent started antidepressants in the first trimester ($n = 381$), 17.9% in the second trimester ($n = 93$), and 9% in the third trimester ($n = 47$). Table 1 also lists the antidepressants taken while breastfeeding. The most commonly used antidepressants during pregnancy and breastfeeding were sertraline, fluoxetine, and paroxetine.

Most of the women described their depression as moderate ($n = 492$; 53.4%), 21.4% ($n = 197$) as severe, 16.1% as mild ($n = 139$), and 10.1% ($n = 93$) as "comes and goes." When asked to describe the effectiveness of the antidepressant, 63% ($n = 574$) described it as very effective, 34% as moderately effective, and only 3.1% as not effective.

Symptoms in newborn infants

Overall, the majority of women reported that their infants never experienced the symptoms of discontinuation syndrome. These findings are listed on Table 2. The most commonly reported symptom was irritability, noted in 25% of infants. A smaller percentage of infants were reported to have inconsolable crying (17%), low body temperature (14%), and significant problems with eating and sleeping (15%).

Logistic regression revealed that mothers who took antidepressants while pregnant and then during breastfeeding were two to eight times more likely to report symptoms of discontinuation syndrome than women who took them only while breastfeeding. These symptoms included jitteriness, vomiting, irritability, low body temperature, inconsolable crying, shivering, and problems with eating and sleeping. Stiffness and moaning were not significantly different. These findings are summarized in Table 3.

As shown in Table 4, infants will have much lower odds of experiencing jitteriness if their mothers took antidepressants during pregnancy with mid-range or long half-lives instead of one with a short half-life. The infants also had lower odds of stiffness if their mothers took antidepressants with long half-lives compared to those infants exposed to an antidepressant with a short half-life.

Timing of antidepressant use during pregnancy also impacted symptoms in neonates. Infants were significantly more likely to experience stiffness if their mothers started taking antidepressants in the second or third trimester compared with those whose mothers started the antidepressant in the first trimester or earlier.

Table 2. Symptoms of Discontinuation Syndrome

Symptom name	Never	Rarely (once per week)	Occasionally (daily)	Several times daily	Total % with symptom
Jitteriness ($n = 494$)	91%	2%	6%	2%	10%
Vomiting ($n = 494$)	90.4%	3%	5%	2%	10%
Irritability ($n = 496$)	76%	8%	11%	6%	25%
Low body temperature ($n = 490$)	86%	8%	4%	2%	14%
Inconsolable crying ($n = 496$)	83%	6%	7%	4%	17%
Shivering ($n = 492$)	95%	3%	1%	1%	5%
Stiffness ($n = 493$)	96%	2%	2%	1%	5%
Moaning ($n = 490$)	96%	2%	1%	1%	4%
Significant eating and sleeping problems ($n = 493$)	87%	3%	5%	5%	13%
Convulsions ($n = 493$)	99.6%	0.1%	0.1%	0.1%	0.3%

Table 3. Odds Ratios for Binary Logistic Regression of Infant Withdrawal Symptoms (for Those Whose Mothers Took Antidepressant During Breastfeeding)

Variable	*Jitteriness* (n = 688)	*Vomiting* (n = 686)	*Irritability* (n = 689)	*Low body temperature* (n = 681)	*Constant inconsolable crying* (n = 690)	*Shivering* (n = 686)	*Stiffness* (n = 688)	*Moaning* (n = 683)	*Eating and sleeping problems* (n = 688)	*Weight gain* (n = 885)
Age[a]	1.015	0.952	0.979	0.977	0.963	0.998	0.974	0.912	0.968	0.964
Education[b]	0.959	0.971	0.986	1.215	1.098	0.961	1.037	1.071	0.943	1.092
Family history[c]	1.927	1.806	1.245	0.968	1.128	2.211	1.558	0.937	1.434	1.285
Severity of depression[d]	1.319	1.393	1.280	1.036	1.302	1.009	2.446**	1.282	1.142	1.086
Taking antidepressant during pregnancy[e]	3.854**	3.384**	2.614***	3.269**	1.666	9.241*	1.727	3.076	2.095*	1.046
−2 log likelihood	175.853	210.392	340.528	228.331	291.066	98.244	107.920	96.691	231.854	403.230
Logistic regression χ^2	16.850**	22.590***	22.670***	15.670**	9.810	11.600*	11.940*	7.820	10.250	5.350
Pseudo R^2	0.046	0.051	0.032	0.033	0.017	0.056	0.052	0.039	0.022	0.007

[a]Age of the mother in years when the baby was born.
[b]Mother's education, where 1 = 8th grade or less, 2 = some high school but did not graduate, 3 = high school graduate or GED, 4 = several years of college, 5 = college Graduate (4 years), and 6 = postgraduate education.
[c]This is a dummy variable: 1 means with depression running in the family, 0 means no family history of depression.
[d]Depression severity, where 0 = no depression, 1 = mild, 2 = moderate, and 3 = severe.
[e]This is a dummy variable: 0 = only took antidepressant during breastfeeding, 1 = took antidepressant during breastfeeding and pregnancy.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Discussion

The present study adds to the literature by providing a large sample and by comparing symptoms in mothers who took antidepressants while both pregnant and later breastfeeding to mothers who only took antidepressants while breastfeeding. The majority of the mothers took SSRIs during pregnancy and breastfeeding. However, other types of antidepressants, such as bupropion and venlafaxine, also accounted for a small portion of antidepressant use.

With regard to the individual symptoms, the overall rate is surprisingly low (on average, about 10% of the mothers reporting symptoms). This incidence is somewhat lower than those found in previous studies. The most common symptoms were irritability, low body temperature, inconsolable crying, and significant eating and sleeping problems. These findings are consistent with the results of Oberlander et al.[6] A smaller percentage of mothers reported symptoms when there was a large sample.

With regard to the multivariate model, six symptoms were approximately two to eight times more likely if mothers took antidepressants while pregnant and later breastfeeding than if mothers took antidepressants only while breastfeeding. These symptoms were jitteriness, vomiting, irritability, low body temperature, shivering, and problems with eating and sleeping. Consistent with our hypotheses, these analyses indicate that there is an effect of using the medication during pregnancy, likely accounting for this difference in symptoms following the withdrawal of medication. One possible explanation for these findings is that the infants' symptoms may have been eased because the mothers were breastfeeding and the infants were receiving a small amount of medication via the milk, making withdrawal more gradual. However, the amount of medication the infants received via breastmilk was not likely enough to completely eliminate symptoms of withdrawal. This is especially true for mothers who were taking SSRIs with short half-lives, such as paroxetine, where there is a more precipitous drop in infant medication levels. Based on our clinical experience, in medications with shorter half-lives, the levels drop quickly after birth compared to medications with longer half-lives. Medications that stay in the infant's system for a longer time after birth may have allowed for a more gradual withdrawal. However, this is difficult to assess in the present study because we only asked the mothers to report only on symptoms that occurred in the first week postpartum.

Study limitations

There were two limitations to our study. First, because the data were collected online, a sampling frame could not be identified ahead of time, nor could refusals be tracked. The sample may have been biased towards more affluent and educated participants, and thus results are likely not representative of all depressed mothers. However, although our sample is likely not representative of all mothers, responses to antidepressants tend to be fairly uniform across demographic categories as long as patients are compliant with their medication regimens. Second, retrospective reporting may have resulted in recall bias, with participants under-reporting, or possibly over-reporting, symptoms. They may have reported fewer symptoms because they were no longer depressed. However, this alone likely would not account for the striking

Table 4. Odds Ratios for Binary Logistic Regression of Infant Withdraw Symptoms (for Those Whose Mothers Took Antidepressant During Breastfeeding and Pregnancy)

	Jitteriness (n = *485*)	*Vomiting* (n = *481*)	*Irritability* (n = *487*)	*Low body temperature* (n = *481*)	*Constant inconsolable crying* (n = *487*)	*Shivering* (n = *483*)	*Stiffness* (n = *484*)	*Moaning* (n = *481*)	*Eating and sleeping problems* (n = *484*)	*Weight gain* (n = *473*)
Age[a]	1.023	0.973	0.997	0.997	0.985	0.990	0.995	0.968	0.988	0.953+
Education[b]	0.993	0.956	0.954	1.156	1.220	0.977	1.103	0.938	0.940	1.112
Family history[c]	2.903	1.607	1.542	1.234	1.313	2.006	3.563	1.133	2.359	1.547
Depression severity[d]	1.202	1.311	1.272	1.043	1.343	1.004	2.318*	1.136	1.106	1.148
Type of antidepressant (reference, long half-life)[e]										
Mid-range half-life	0.305*	1.146	0.720	0.824	0.635	0.855	0.364	0.426	0.804	1.547
Long half-life	0.462	0.805	0.849	0.820	0.624	0.555	0.284*	0.613	0.826	1.072
Trimester of starting antidepressant (reference: first trimester or earlier)										
Second trimester	1.185	1.590	0.729	1.309	1.165	0.954	2.737	0.785	0.969	0.883
Third trimester	1.008	0.802	1.211	1.858	0.487	1.060	4.007*	1.667	1.325	1.447
−2 log likelihood	148.489	174.832	268.087	190.473	218.716	91.211	79.888	81.658	182.604	216.977
Logistic regression χ^2	11.710	8.390	7.660	3.730	10.420	2.510	19.210*	3.050	5.300	8.510
Pseudo R^2	0.038	0.023	0.014	0.010	0.023	0.014	0.107	0.018	0.014	0.019

[a]Age of the mother in years when the baby was born.
[b]Mother's education, where 1 = 8th grade or less, 2 = some high school but did not graduate, 3 = high school graduate or GED, 4 = several years of college, 5 = college graduate (4 years), and 6 = postgraduate education.
[c]This is a dummy variable: 1 means with depression running in the family, 0 means no family history of depression.
[d]Depression severity, where 0 = no depression, 1 = mild, 2 = moderate, and 3 = severe.
[e]We categorized antidepressants into those with a long half-life (including fluoxetine and sertraline), short half-life (including paroxetine), and mid-range half-life (others).
*$p < 0.05$.

and consistent difference in symptoms of neonates whose mothers took antidepressants during pregnancy versus those who took them only while breastfeeding. Over-reporting also seems unlikely given these same consistent differences.

Clinical strategies

Women taking antidepressants during their last trimester should be warned of possible discontinuation syndrome so they can manage this syndrome proactively. One possible course is to taper medications at the end of their pregnancies, although some warn that the risk of relapse outweighs the risk of discontinuation syndrome.[8] If mothers opt to taper their medications, they should be warned that pregnant women are especially prone to relapse of depressive symptoms and should be monitored carefully for symptoms of depression.[8] Another option is to switch to a longer-acting agent, such as fluoxetine or sertraline. If women are taking a medication with a shorter half-life, clinicians delivering their babies should be appraised so they can manage discontinuation symptoms.

Conclusions

The results of our study indicate that symptoms of discontinuation syndrome occur in infants of women who take antidepressants during pregnancy. However, the overall percentage of infants with these symptoms appears to be low. Irritability was the most common symptom, affecting 25% of the infants in the study. As predicted, discontinuation symptoms are significantly higher in women who took antidepressants during pregnancy and subsequently breastfed their infants compared to those mothers took antidepressants only during breastfeeding. Symptoms of discontinuation syndrome, when they occur, tend to be mild and self-limiting and can be managed with supportive care.

Disclosure Statement

No competing financial interests exist.

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