Neonate Characteristics After Maternal Use of Antidepressants in Late Pregnancy

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Background: Exposure to antidepressants during the third trimester of pregnancy has been associated with an increased risk for adverse birth outcomes, including preterm birth, respiratory distress, and hypoglycemia.

Objective: To investigate neonatal outcomes in 997 infants (987 mothers) after maternal use of antidepressants based on prospectively recorded information in antenatal care documents.

Results: An increased risk for preterm birth (odds ratio [OR], 1.96) and low birth weight (OR, 1.98) was verified, but the gestational week-specific birth weight was increased notably after exposure to tricyclic antidepressants. An increased risk for a low Apgar score (OR, 2.33), respiratory distress (OR, 2.21), neonatal convulsions (OR, 1.90), and hypoglycemia (OR, 1.62) was found, the latter especially after exposure to tricyclic drugs, but no significant effect on the frequency of neonatal jaundice was seen (OR, 1.13). Most effects seemed not to be selective serotonin reuptake inhibitor drug specific, and outcomes after exposure to paroxetine hydrochloride were not worse than after exposure to other selective serotonin reuptake inhibitors.

Conclusions: Neonatal effects after maternal use of antidepressant drugs during late pregnancy were seen. Selective serotonin reuptake inhibitors may be the drugs of choice during pregnancy.

Arch Pediatr Adolesc Med. 2004;158:312-316

SOME STUDIES1-8 HAVE BEEN PUBLISHED ON THE OCCURRENCE OF BIRTH DEFECTS AFTER MATERNAL USE OF ANTIDEPRESSANTS WITHOUT ANY CERTAIN TERATOGENIC EFFECT BEING DEMONSTRABLE. LESS IS PUBLISHED ON THE NEONATAL OUTCOME BEIDES BIRTH DEFECTS, AND PUBLISHED STUDIES ARE ALL SMALL. MOST STUDIES4,7,9 HAVE FOUND EVIDENCE FOR INCREASED RATES OF PREMATURE DELIVERY; ADMISSION TO SPECIAL-CARE NURSERIES; POOR NEONATAL ADAPTATION, INCLUDING RESPIRATORY DIFFICULTIES; LOW APTER SCORIS; HYPOGLYCEMIA; CYANOSIS ON FEEDING; AND CEREBRAL EXCITATION. ONE OF THE STUDIES9 SUGGESTED A SPECIFICALLY POOR OUTCOME AFTER TREATMENT WITH PAROXETINE HYDROCHLORIDE. ANOTHER RECENT STUDY6 FOUND NO ILL EFFECTS OF MATERNAL USE OF TRICYCLIC DRUGS, BUT DID FIND ILL EFFECTS FOR USE OF SOME SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS). HEALTHY NEURODEVELOPMENT HAS BEEN FOUND IN 2 STUDIES,7,10 BUT RECENTLY, AN INCREASED RISK FOR AN ABNORMAL BOEL TEST RESULT AT THE AGE OF 7 TO 10 MONTHS WAS DESCRIBED, BASED ON 7 SUCH OUTCOMES.11

The present study was performed to investigate neonatal abnormalities using prospectively collected cases, large enough to give reasonably adequate risk estimates and to allow a comparison of different antidepressant drugs.

Methods

Data were obtained from the Swedish Medical Birth Registry. Since July 1, 1994, information on maternal drug use during pregnancy has been collected prospectively.12 From July 1, 1995, the records of all women delivered of a neonate should contain information on drug use. Children born between July 1, 1995, and December 31, 2001, were, therefore, selected for study.

The Swedish Medical Birth Registry13,14 contains data from copies of medical documents from the antenatal care that practically all pregnant women receive. Data on first-trimester exposures are obtained by midwife interviews at the first antenatal care visit (usually week 10-12), while data on later exposures are obtained from the copies of the medical records of the antenatal care. By using the latter, infants whose mothers had been prescribed an antidepressant drug after the first visit to the antenatal care center were identified. For most of the cases, the drug dosage and the date of starting and stopping were recorded.

The Swedish Medical Birth Registry also contains data on delivery and the newborn, obtained from copies of the medical records used at delivery and at the pediatric examination of the newborn.13,14 In the present study, the following variables were used: maternal age, parity (number of previously born infants plus 1),
Table 1. Background Data on Women Using Antidepressants in Late Pregnancy and All Women Giving Birth

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women Using Antidepressants in Late Pregnancy</th>
<th>All Women Giving Birth</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13-19</td>
<td>8</td>
<td>11,293</td>
<td>0.18 (0.08-0.42)</td>
</tr>
<tr>
<td>20-24</td>
<td>107</td>
<td>88,086</td>
<td>0.81 (0.65-1.02)</td>
</tr>
<tr>
<td>25-29</td>
<td>265</td>
<td>200,654</td>
<td>1.00‡</td>
</tr>
<tr>
<td>30-34</td>
<td>340</td>
<td>184,683</td>
<td>1.33 (1.12-1.56)</td>
</tr>
<tr>
<td>35-39</td>
<td>217</td>
<td>75,119</td>
<td>1.86 (1.54-2.25)</td>
</tr>
<tr>
<td>40-44</td>
<td>48</td>
<td>13,354</td>
<td>2.23 (2.63-3.08)</td>
</tr>
<tr>
<td>≥45</td>
<td>2</td>
<td>539</td>
<td>2.60</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>403</td>
<td>244,017</td>
<td>1.00‡</td>
</tr>
<tr>
<td>2</td>
<td>302</td>
<td>208,146</td>
<td>0.81 (0.70-0.94)</td>
</tr>
<tr>
<td>3</td>
<td>155</td>
<td>83,272</td>
<td>0.80 (0.66-0.97)</td>
</tr>
<tr>
<td>≥4</td>
<td>127</td>
<td>38,448</td>
<td>1.06 (0.85-1.32)</td>
</tr>
<tr>
<td>Smoking in early pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>39</td>
<td>37,952</td>
<td>NA</td>
</tr>
<tr>
<td>No</td>
<td>647</td>
<td>462,645</td>
<td>1.00‡</td>
</tr>
<tr>
<td>&lt;10 cigarettes/d</td>
<td>159</td>
<td>48,632</td>
<td>2.39 (2.01-2.64)</td>
</tr>
<tr>
<td>≥10 cigarettes/d</td>
<td>142</td>
<td>24,654</td>
<td>3.95 (3.04-4.72)</td>
</tr>
<tr>
<td>Cohabitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>30</td>
<td>34,391</td>
<td>NA</td>
</tr>
<tr>
<td>Yes</td>
<td>834</td>
<td>512,102</td>
<td>1.00‡</td>
</tr>
<tr>
<td>No</td>
<td>123</td>
<td>27,390</td>
<td>2.05 (1.69-2.50)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, data not applicable; OR, odds ratio.
*Data are given as number of women.
†Data compare the 2 groups of women. Each variable was adjusted for all other variables.
‡Reference.

distributions. In this situation, comparisons between groups were made with Fisher exact tests.

RESULTS

OVERVIEW

A total of 997 infants whose mothers received antidepressant therapy after the first antenatal care center visit were identified. Among the 987 mothers, 395 had used tricyclic drugs (including imipramine hydrochloride [n=333] and amitriptyline hydrochloride [n=58]), 558 had used SSRIs (including citalopram [n=285], paroxetine [n=106], fluoxetine hydrochloride [n=91], and sertraline hydrochloride [n=77]), and 63 had used other antidepressants (including venlafaxine hydrochloride [n=24]). There were 31 women who had used 2 antidepressants during late pregnancy; 19 of them had used a tricyclic drug and an SSRI and 8 had used an SSRI and an antidepressant other than a tricyclic drug or another SSRI.

The pregnancy weeks when the drug had been used were not stated in 387 cases; in 70 cases, drug use stopped before week 24, and in 561 cases, drug use started after or continued past week 23.

Table 1 presents some background data for the women using antidepressants and for the total population of women giving birth.

GESTATIONAL DURATION, BIRTH WEIGHT, AND FETAL GROWTH

These variables were studied only in singleton births. The OR for preterm birth (Table 2) was increased, and amounts to about 2, similar for different subgroups. There was no statistically significant difference between the ORs when the woman had used a tricyclic drug and when she had used an SSRI (z=0.97, P=.25).

The OR for low birth weight (Table 2) was also around 2, and similar between groups (comparison of the tricyclic antidepressant group vs the SSRI group, z=0.20, P=.39). This indicates no increase in the risk for small for gestational age, as was also seen in Table 2. On the other hand, there was an increased risk for large for gestational age that, however, did not reach statistical significance.

In a previous article, a differential effect was described in smoking and nonsmoking women on fetal growth based on first-trimester exposures to antidepressant drugs. The study of large for gestational age was, therefore, repeated and restricted to nonsmoking women. The OR increased only slightly and was still not statistically significant (for all infants: OR, 1.26; 95% CI, 0.93-1.69).

When the mean and standard error of the mean of standard deviation score of the birth weight in singleton term infants was studied, a highly significant increase was seen for all infants exposed to antidepressants (score, 0.14±0.04; t=4.0, P=.001), stronger for nonsmokers (score, 0.17±0.04; t=3.9, P=.001) than for smokers (score, 0.09±0.07; t=1.32, P=.17). The effect of exposure to tricyclic antidepressants among nonsmokers was stronger (mean±SEM score, 0.23±0.07; t=3.2, P=.002) than the effect of exposure to SSRIs without tricyclic antidepressants (mean±SEM score, 0.12±0.06).
Table 2. Preterm Delivery, Low Birth Weight, SGA, and LGA Data for Only Singleton Births

<table>
<thead>
<tr>
<th>Group*</th>
<th>Preterm Delivery (&lt;37 wk)</th>
<th>Low Birth Weight (&lt;2500 g)</th>
<th>SGA (&lt;2 SDs)</th>
<th>LGA (&lt;2 SDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>OR (95% CI)‡</td>
<td>Yes</td>
</tr>
<tr>
<td>Total population</td>
<td>28634</td>
<td>535022</td>
<td>1.00§</td>
<td>18377</td>
</tr>
<tr>
<td>All antidepressants</td>
<td>101</td>
<td>875</td>
<td>1.96 (1.60-2.41)</td>
<td>69</td>
</tr>
<tr>
<td>≥24 wk</td>
<td>58</td>
<td>486</td>
<td>2.02 (1.54-2.63)</td>
<td>35</td>
</tr>
<tr>
<td>Tricyclic drugs</td>
<td>49</td>
<td>351</td>
<td>2.50 (1.87-3.34)</td>
<td>27</td>
</tr>
<tr>
<td>SSRIs</td>
<td>60</td>
<td>492</td>
<td>2.06 (1.58-2.69)</td>
<td>40</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age; SSRI, selective serotonin reuptake inhibitor.

*The total population indicates all women giving birth; all antidepressants, women using any antidepressant during pregnancy; ≥24 wk, women with known exposure to an antidepressant after pregnancy week 23; tricyclic drugs, women using tricyclic drugs during pregnancy; SSRIs, women using SSRIs during pregnancy.

†Data are given as number of neonates.
‡Data compare the total population group with the all antidepressants group after adjustment for year of birth, maternal age, parity, and maternal smoking in early pregnancy.
§Reference.

INFANT DIAGNOSES

There was a rather strong and statistically significant increase in the OR for respiratory distress (Table 3). This was slightly higher after the use of tricyclic antidepressants than after the use of SSRIs, but the difference may well be random (z=1.31, P=.17). After exclusion of preterm births (<37 weeks), the OR was somewhat reduced but still highly significant (1.81; 95% CI, 1.37-2.40).

There was no significant effect on the rate of neonatal jaundice (Table 3), which was nonsignificantly increased after the use of tricyclic antidepressants but not after the use of SSRIs.

For neonatal hypoglycemia (Table 3), a significantly increased OR was seen, which again was stronger after the use of tricyclic antidepressants than after the use of SSRIs, but this difference may be random (z=1.43, P=.14).

The OR for low Apgar score (in term singleton infants) was increased after the use of antidepressant drugs, with about the same magnitude for tricyclic drugs and SSRIs (Table 3).

Neonatal convulsions (Table 3) were registered more often with than without antidepressant drugs, and the risk ratio was higher after the use of tricyclic antidepressants than after the use of SSRIs, but the difference may be random (Fisher exact test, P=.50). The frequency of a diagnosis of cerebral excitation was also higher with than without antidepressants, but the difference did not reach statistical significance (OR, 1.22; 95% CI, 0.91-1.65) and was higher after the use of tricyclic drugs (OR, 1.45; 95% CI, 0.93-2.25) than after the use of SSRIs (OR, 1.07; 95% CI, 0.70-1.62), but these 2 estimates do not differ significantly (z=0.96, P=.35).

A special study was made of paroxetine exposure compared with exposure to other SSRIs (Table 4). Only
crude comparisons were made (without adjustment for year of birth, maternal age, parity, or maternal smoking) because numbers were low and comparisons were made within SSRIs, where confounding factors should be roughly equal. Paroxetine exposure gave higher ORs than exposure to other SSRIs for some conditions, but none reached statistical significance.

USE OF OTHER DRUGS

Women who used antidepressants used other drugs in excess. Table 5 lists the number of women using other drug categories. Exclusion in the analysis of women who had used any one of these drugs did not reduce the estimated ORs. For preterm births, the OR changed from 1.96 to 2.01 (95% CI, 1.17-3.46), and for all infant diagnoses (given in Table 2), from 1.96 to 2.15 (95% CI, 1.26-3.66). The rate of anticonvulsant users is high (1.6% vs the population rate of 0.3%), but among the infants of the 16 women using anticonvulsants, none experienced neonatal convulsions. Of the mothers of infants with convulsions, 3 had used other psychoactive drugs (1 expected), 1 had used insulin, and 2 had used antiasthmatic drugs.

COMMENT

This study has certain advantages: a reasonably large number of cases could be studied and information on drug use is based on medical record information and is prospective related to the outcome. Outcomes could be compared with the corresponding outcomes among all infants born with adjustment for some confounders. The study is large enough to give information also on relatively rare events and to compare the effects of different anticonvulsants. It is more than twice the size of the largest previously published study.

There are also disadvantages. The exact time of administration of the drugs was not specified in about 40% of the cases. When specified, few stopped drug use before week 24 (11.5%). In all the tables, the ORs for all case subjects and for those case subjects in whom exposure was known to have occurred after week 23 were shown and no major differences exist. It is, therefore, likely that when no timing was stated, most women had actually used the drugs after week 23. Furthermore, the medical record note indicates that the drug has been prescribed, not that the woman necessarily took it. If some did not, this will bias the estimated ORs toward unity.

There were clear-cut effects on pregnancy outcome after maternal use of antidepressants. For most conditions, there seems to be no certain difference between women using tricyclic drugs, SSRIs, or other antidepressants, even though there is a common tendency for tricyclic drugs to show higher ORs than SSRIs. One explanation for this could be that the effects on the outcome were actually due to residual confounding from the maternal disease or something linked to the disease. Even if most women using antidepressants were probably in a depressive state, these drugs (notably SSRIs) are used for other psychiatric conditions as well. Women using antidepressants may use other drugs, alcohol, or illicit drugs in excess. The exclusion of such drugs being reported did not reduce the risk estimates; illicit drug use especially is probably underreported. Illicit drug use among women who give birth is relatively rare in Sweden. Especially for gestational duration and birth weight, maternal smoking is of importance. Adjustment for maternal smoking in early pregnancy was made, but this may be insufficient for 2 reasons. One is that the classification of smoking is relatively crude and the upper group (≥10 cigarettes per day) is open and may include different proportions of heavy smokers who will not be adjusted for. Furthermore, maternal smoking in late pregnancy is more important for fetal growth and neonatal diagnoses than smoking in early pregnancy, and women with psychiatric symptoms may stop smoking during pregnancy to a lesser degree than healthy women. One main effect of maternal smoking is fetal growth retardation, and no effect on the rate of small for gestational age neonates was seen in the study, which speaks against a confounding by uncontrolled smoking habits.

Another explanation for the similarities in outcome irrespective of drug type used could be that the various drugs can have common pharmacological mechanisms.

Previously, it was found that infants born after early...
Maternal use of antidepressants and notably SSRIs has been associated with neonatal complications because of withdrawal reactions. Recently, paroxetine has been pinpointed as causing more problems than other SSRIs.

By studying 907 infants whose mothers had used antidepressants during the latter part of the pregnancy, an excess of neonatal problems could be confirmed, if anything more pronounced after tricyclic drug use than after SSRIs use, but no difference between paroxetine and other SSRIs could be demonstrated.

exposure to non–SSRI antidepressants (mainly tricyclic drugs) were heavier than expected when the mother did not smoke, but that was not the case after exposure to SSRIs. The present study confirms this finding, although in a less clear-cut way.

The earlier observations15 of an increased risk for neonatal respiratory distress and for neonatal hypoglycemia could be verified; however, an increased risk for neonatal jaundice could not be verified. For respiratory distress, neonatal hypoglycemia, and neonatal convulsions, tricyclic drugs showed a higher OR than SSRIs did, but these differences could be random, despite the relatively large number of exposed infants. The effect on hypoglycemia is absent after exposure to SSRIs, but is statistically significant after exposure to tricyclic antidepressants.

There was no evidence that exposure to paroxetine was more harmful than exposure to other SSRIs, but the numbers were small—yet, the total number of exposures to paroxetine is about twice the number previously reported.9 There were 7 cases of respiratory distress among 109 infants exposed to paroxetine, while Costei et al9 found 9 cases among 55 similarly exposed infants. This is not quite significant difference (P = .05) could mirror different criteria for and certainty of this diagnosis, but in the Swedish Medical Birth Register, this diagnosis occurs in about 3% of all infants (Table 3), which is compatible with the 1 in 54 rate in the control material of Costei et al. An increased risk for respiratory distress after third trimester exposure to fluoxetine has also been described.4 This effect is probably a general effect of antidepressant drugs, underlying disease, or something closely related, and is not specific to paroxetine.

The symptoms observed among the neonatal infants could be expressions of withdrawal symptoms. Such symptoms should begin a few days after birth. We have no detailed information on the days of occurrence of, for instance, neonatal convulsions. In a study17 of World Health Organization adverse reaction reports after exposure to SSRIs in adults, paroxetine seemed to cause withdrawal symptoms more frequently than other SSRIs. This article also described a higher ratio of central nervous system–psychiatric withdrawal symptoms for paroxetine and sertraline vs fluoxetine. The article is based on spontaneously reported adverse events that may not be representative of actually occurring events.

One observation of a possible difference between tricyclic antidepressants and SSRIs refers to the occurrence of hypoglycemia. The higher birth weight after the use of tricyclic antidepressants than after the use of SSRIs was suggested to be related to the capability of the former drugs to cause hyperglycemia (ie, a diabetogenic effect).18 Fetal hyperinsulinism resulting in neonatal hypoglycemia could be the result. The use of tricyclic antidepressants in early pregnancy has been observed to be associated with an increased risk for cardiac defects in the infant19—malformations known to be associated with maternal diabetes mellitus.

In conclusion, certain anomalies can be found in the outcome after the use of antidepressant drugs in late pregnancy. To some extent, these may be the result of the underlying disease or of factors associated with the disease, but a direct drug effect is likely, at least partly as withdrawal symptoms. If anything, outcome seemed more unfavorable after the use of tricyclic drugs than after the use of SSRIs, which perhaps should be the drugs of choice during pregnancy.

Accepted for publication September 23, 2003.

This study was supported by a grant from the K. A. Wallenberg Foundation, Stockholm, Sweden.

I obtained permission to access the Swedish Medical Birth Register from the National Board of Health, Stockholm, Sweden.

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REFERENCES