Amniotic Fluid and Umbilical Cord Blood Concentrations of Antidepressants in Three Women

Amy Hostetter, James C. Ritchie, and Zachary N. Stowe

Background: Pregnancy and the postpartum period are a time of increased risk for women to develop mood disorders. As such, the reproductive safety data on antidepressant use during pregnancy have rapidly expanded over the last decade; however, there is relatively sparse information on maternal/fetal exchange of these medications and no data reporting their concentrations in amniotic fluid.

Methods: We report on three women treated during pregnancy with fluvoxamine, sertraline, and venlafaxine, respectively. Amniotic fluid at amniocentesis and umbilical cord blood and maternal blood at delivery were collected and analyzed for antidepressant concentrations using high performance liquid chromatography with UV detection.

Results: Antidepressant and metabolite concentrations were detectable in all amniotic fluid samples, though parent compound concentrations were less than maternal serum and umbilical cord blood concentrations. No adverse effects of the medication were reported.

Conclusions: The presence of these antidepressants in amniotic fluid suggests that fetal exposure to these medications is continual and may occur through a variety of paths, thus accounting for increased fetal exposure. These paths include circulatory via placental passage, gastrointestinal via fetal swallowing, and respiratory secondary to fetal lung absorption. Biol Psychiatry 2000;48:1032–1034 © 2000 Society of Biological Psychiatry

Key Words: Amniotic fluid, umbilical cord, placental passage, antidepressant, pregnancy

Introduction

The extant literature on the reproductive safety of antidepressant medications has rapidly expanded over the past decade, though remarkably sparse information on the actual maternal/fetal exchange of these medications has been reported. A literature search (Medline 1960–1999) failed to identify any publications documenting human amniotic fluid concentrations of antidepressants; however, other studies have quantified human amniotic fluid concentrations of anticonvulsants (Meyer et al 1988; Omtzigt 1992), fentanyl (Shannon et al 1998), nicotine (Luck and Nau 1984), and various antibacterial agents (Pacifici and Nottoli 1995).

The amniotic fluid is produced in part by the amniotic cells, but is derived primarily from maternal blood (Sadler 1985). The composition of amniotic fluid varies with gestational time. In later pregnancy, the fluid includes fetal urine and lung liquid secretion. Drugs excreted by the fetal kidney enter the amniotic fluid and recirculate due to fetal swallowing (Morgan 1997).

This report describes three cases of antidepressant use during pregnancy with collection of both amniotic fluid during amniocentesis and umbilical cord blood at delivery. All women received a comprehensive risk–benefit assessment and were treated throughout their pregnancies at the Emory University Pregnancy and Postpartum Mood Disorders Program. Amniocentesis was planned as part of their obstetric care secondary to advanced maternal age in all three cases. Additional amniotic fluid (0.5 mL) and umbilical cord blood (3 mL) were collected at the subject’s request to provide some measure of medication exposure.

Case A

Mrs. A is a 34-year-old married, white female treated with fluvoxamine 100 mg once daily for severe anxiety and obsessive thinking. Mrs. A presented at 11 weeks gestation; her pregnancy was planned, and she conceived while taking the medication. An amniocentesis was performed at 16 weeks gestation. At 29 weeks gestation the fluvoxamine was increased to 150 mg once daily secondary to increased anxiety. At 40 weeks gestation Mrs. A had an uncomplicated vaginal delivery of a female infant who weighed 3.23 kg and had appearance, pulse, grimace, activity, respiration (APGAR) scores of 8 and 9.
Case B

Mrs. B is a 40-year-old married, white female treated with sertraline monotherapy 150 mg/day for major depression. Mrs. B conceived on this dose of sertraline, and the pregnancy progressed without complication. At 17 weeks gestation the patient underwent amniocentesis. At 37.6 weeks gestation the patient’s dose was increased to 175 mg once daily secondary to increased depressive symptoms. At 39 weeks gestation Mrs. B had an uncomplicated vaginal delivery of a female infant who weighed 3.66 kg and had APGAR scores of 9 and 9.

Case C

Mrs. C is a 40-year-old married, white female who presented at 15 weeks gestation with a twin pregnancy. Before becoming pregnant she was being treated with venlafaxine, 100 mg twice daily (b.i.d), for depression and anxiety. It was a planned pregnancy and she had tapered off the venlafaxine before conception. She reported symptom recurrence at 6 weeks gestation. At 15 weeks gestation the patient underwent amniocentesis. At 36 weeks gestation the patient’s dose was increased to 175 mg once daily secondary to increased depressive symptoms. At 39 weeks gestation Mrs. C had an uncomplicated delivery of a female infant who weighed 3.66 kg and had APGAR scores of 9 and 9.

Case D

Mrs. D is a 40-year-old married, white female treated with fluoxetine 80 mg/day for major depression. Mrs. D conceived on this dose of fluoxetine, and the pregnancy progressed without complication. At 17 weeks gestation the patient underwent amniocentesis. At 37.6 weeks gestation the patient’s dose was increased to 150 mg once daily secondary to increased depressive symptoms. At 39 weeks gestation Mrs. D had an uncomplicated vaginal delivery of a female infant who weighed 3.66 kg and had APGAR scores of 9 and 9.

Methods and Materials

All three subjects were recruited from the Emory Pregnancy and Postpartum Mood Disorders Program for participation in the current case series. Written informed consent was obtained for collection of maternal serum and umbilical cord blood and the use of data obtained from manuscripts on other biological samples (such as amniotic fluid and placental tissue) in submission.

The quantification of parent compound and metabolite concentrations in the above samples was accomplished, following a solid-phase extraction, by isocratic high performance liquid chromatography (HPLC) with UV detection. High performance liquid chromatography separation was performed using a 100 × 2 mm stainless steel Keystone Scientific (Bellefonte, PA) MOS 2 Hypersil (C8) reverse phase column, particle size 3 μm. Analysis was conducted with a Hewlett Packard (Palo Alto, CA) HPLC chemstation equipped with a computer, a series 1100 degasser, quaternary pump, autosampler, and diode array detector, as detailed in previous reports (Stowe et al 1997, 2000).

The limit of detection of parent compounds and metabolites was 2.0 ng/mL.

Results

Fluvoxamine and venlafaxine were detectable in amniotic fluid; sertraline was below the limit of detection. All parent compounds were found in umbilical cord samples. Similarly, the metabolites of sertraline and venlafaxine were detectable in both amniotic fluid and umbilical cord blood. The data are shown in Table 1. In all cases, the women had taken a stable dose of antidepressant for uncomplicated deliveries, and no adverse effects of medication exposure were reported.

Table 1. Antidepressant Concentrations in Amniotic Fluid, and Maternal and Umbilical Cord Serum

<table>
<thead>
<tr>
<th></th>
<th>Fluvoxamine (ng/mL)</th>
<th>Sertraline (ng/mL)</th>
<th>Desmethylsertraline (ng/mL)</th>
<th>Venlafaxine (ng/mL)</th>
<th>O-Desmethylvenlafaxine (ng/mL)</th>
<th>Weeks Gestation</th>
<th>Hours after maternal dose</th>
</tr>
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<tbody>
<tr>
<td>Case A</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>Amniotic fluid</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>100</td>
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<tr>
<td>Maternal serum</td>
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<td></td>
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<td>150</td>
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<tr>
<td>Cord blood</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
<td>150</td>
</tr>
<tr>
<td>Case B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Maternal serum</td>
<td>53</td>
<td>349</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>150</td>
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<tr>
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<td></td>
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<td></td>
<td>17</td>
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<td>194</td>
<td></td>
<td></td>
<td></td>
<td>39</td>
<td>175</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>97</td>
<td></td>
<td></td>
<td>36</td>
<td>300</td>
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<td>Amniotic fluid</td>
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<td></td>
<td></td>
<td></td>
<td>36</td>
<td>300</td>
</tr>
<tr>
<td>Cord blood twin A</td>
<td>584</td>
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<td></td>
<td></td>
<td></td>
<td>36</td>
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<tr>
<td>Cord blood twin B</td>
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<td>325</td>
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<td></td>
<td></td>
<td>36</td>
<td>300</td>
</tr>
</tbody>
</table>

NO, not obtained.
greater than five half-lives of elimination before amniocentesis and delivery. All samples were collected when serum levels had reached steady state; however, times after maternal dose at sampling varied by case and may influence antidepressant concentrations. Information on the maternal/fetal exchange of venlafaxine (Case C) is limited, as maternal blood was not obtained at the time of amniocentesis, and the amniocentesis was performed after 2 weeks of treatment with venlafaxine, as opposed to 4 months for Cases A and B.

Discussion

These novel data demonstrate that antidepressants are present in amniotic fluid, though in lower concentrations than maternal serum and umbilical cord blood. The presence of these antidepressants in amniotic fluid provides an additional pathway of continuous fetal exposure. Therefore, exposure via maternal circulation/placental passage may not account for total exposure. These data may explain the results in a preliminary rat study conducted by our group (Owens et al 1998). Briefly, in a series of five pregnant rats treated with selective serotonin reuptake inhibitors (SSRIs) via osmotic minipumps the pups were delivered by cesarean section and had brain concentrations that were 50–75% of the maternal brain concentration in ng/mg protein. These laboratory results are very preliminary but suggest that “in utero” exposure can result in higher, if not frankly therapeutic, central nervous system exposure to antidepressants. The long-term consequences of such exposure are unknown. In the current case series, it is reassuring that there were no obstetric complications or acute adverse effects noted in the four infants.

For Case A (fluvoxamine), maternal serum at the time of delivery was lower than at the time of amniocentesis, despite an increase in dose. Clearly the maternal serum concentrations 18 hours after dose at amniocentesis (41 ng/mL), while the samples were obtained 30 hours after dose at delivery (7 ng/mL), may reflect a more rapid circulatory clearance of fluvoxamine relative to its appearance in amniotic fluid. Another potential contributing factor is the impact of the physiologic changes of later pregnancy on the metabolism of the medications, potentially yielding a decreased serum concentration (Redmond 1985). All three women in this case series required an increase of their daily medication dose in the third trimester to maintain symptom control. This is consistent with our report on the dose of SSRIs across pregnancy, which demonstrated that two thirds of subjects require an increase in dose during pregnancy to maintain euthymia (Hostetter 2000). The tendency for antidepressant dose increases during pregnancy underscores the importance of studies designed to determine the amount of fetal exposure to psychotropic medications.

When one considers the expanding data, incidence of psychiatric illness in women of reproductive years, and the broadening use of SSRIs, one realizes there is a need to assess concerns of accumulation in the fetal circulation and, more importantly, in fetal brain tissue. Expansion of such data will provide a method for comparing fetal exposure between medications both for clinical treatment planning and designing long-term infant follow-up studies.

References


