

Antidepressants in Amniotic Fluid: Another Route of Fetal Exposure

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Objective: The authors' goal was to determine the concentration of antidepressants in amniotic fluid during maternal treatment of depression.

Method: Women treated with antidepressants undergoing amniocentesis for obstetrical reasons were enrolled. Antidepressant concentrations in amniotic fluid and maternal serum were determined with high-performance liquid chromatography.

Results: Amniotic fluid was obtained from 27 women, and the amniotic fluid's antidepressant concentrations were highly variable. For the parent compounds, the amniotic fluid concentrations of selective serotonin uptake inhibitors averaged 11.6% (SD=9.9%) of maternal serum concentrations (N=22). Amniotic fluid to ma-

ternal serum ratios were higher for venlafaxine: 172% (SD=91%) (N=3). Of interest, the amniotic fluid to maternal serum ratios for the metabolites (N=19) did not demonstrate a consistent pattern compared to the parent compound ratios. In 10 subjects, the amniotic fluid to maternal serum ratio for the metabolites was higher than the parent compound and lower in the remaining nine subjects.

Conclusions: The pattern of antidepressant concentrations in amniotic fluid is similar to recent data for placental passage. Although the significance of amniotic fluid exposure remains to be determined, these results demonstrate that maternally administered antidepressants are accessible to the fetus in a manner not previously appreciated.

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Antidepressant use during pregnancy has undergone considerable scrutiny in the past decade. Despite increasing interest in defining drug transfer between mother and fetus, some pathways of fetal exposure have been incompletely investigated. One route of fetal exposure for which especially sparse information exists is amniotic fluid. Previous investigations have examined amniotic fluid concentrations of anticonvulsants (1, 2), antibiotics (3), and nicotine (4), but only a single report exists on antidepressants (5), to our knowledge.

One important consideration is that amniotic fluid composition varies with gestational age and evolving rates of fetomaternal exchange. In early pregnancy, amniotic fluid is predominantly an ultrafiltrate of maternal serum. In later pregnancy, however, fetal urine is the principal constituent of amniotic fluid. Amniotic fluid is not only derived from varied sources, but it also reaches the fetus via several routes, including 1) inhalation into the respiratory tract, bypassing fetal first-pass hepatic metabolism; 2) swallowing into the gastrointestinal tract; and 3) possibly transcutaneous absorption. The fetus swallows 7 ml/day of amniotic fluid at 16 weeks' gestation, increasing to 16 ml/day by 20 weeks' gestation, and peaking at 210–760 ml/day by term (6). If amniotic fluid contains significant antidepressant quantities, amniotic fluid may represent a medium for continuous fetal exposure to maternally administered drugs and metabolites.

Method

The present study is a naturalistic prospective investigation of antidepressant concentrations in the amniotic fluid of 27 women treated with a fixed antidepressant dose (citalopram [N=1], escitalopram [N=1], fluoxetine [N=12], fluvoxamine [N=1], paroxetine [N=2], sertraline [N=6], and venlafaxine [N=4, including one set of twins]) for more than 4 weeks before amniocentesis. All women underwent amniocentesis as part of recommended obstetrical care and gave written informed consent for retention and analysis of amniotic fluid and serum samples. Twenty-three women underwent amniocentesis between 14 and 21 weeks' gestation because of advanced maternal age. Amniocentesis was performed for four women proximate to delivery to verify fetal lung maturity before induction. Maternal serum was collected within 14 days of amniocentesis for the majority (N=25) of the 27 subjects. Obstetrical outcome data were collected by self-report from all participants who had delivered before preparation of this article. This study was approved by the institutional review board of Emory University School of Medicine.

Isocratic high-performance liquid chromatography with ultraviolet detection was used to quantify parent drug and active metabolite (norfluoxetine, desmethylsertraline, *O*-desmethylvenlafaxine) concentrations in paired maternal serum and amniotic fluid samples. Metabolite concentrations for citalopram and escitalopram were not determined in the present study secondary to the manufacturers declining to provide the internal standards for such metabolites. After solid-phase extraction of samples, high-performance liquid chromatography separation was accomplished by using a 100×2-mm stainless steel Keystone Scientific (Bellefonte, Pa.) MOS-2 Hypersil (C8) reverse-phase column of 3 μm particle size. Chromatographic data were analyzed by using a computer-controlled Hewlett Packard (Palo Alto, Calif.)

high-performance liquid chromatography chemstation incorporating a degasser, an autosampler, and a diode array detector. The limit of detection was 2.0 ng/ml. Amniotic fluid concentrations below the limit of detection were converted to 2.0 ng/ml to avoid underestimating fetal exposure.

A descriptive analysis was conducted by the calculation of means, standard deviations, and ranges for the parent drug and metabolite concentrations in both maternal serum and amniotic fluid. Simple correlation analysis was performed to evaluate the relationship between maternal serum and amniotic fluid concentrations. The ratio of the medication (and metabolite) concentration in amniotic fluid versus that in maternal serum was also calculated for paired samples (25 of 27).

Results

A total of 28 women were enrolled in the study. Data for one participant, for whom the parent compound was undetectable in both maternal serum and amniotic fluid, was excluded from analysis because medication compliance could not be confirmed. The remaining results are reported on 27 subjects with confirmed antidepressant exposure (Table 1, published in the online version of this article).

Parent compounds were detected in all of the amniotic fluid samples for four of seven antidepressants (citalopram, escitalopram, fluvoxamine, and venlafaxine). Fluoxetine was detectable in 11 of 12 fluid samples, paroxetine was detectable in one of two fluid samples, and sertraline was detectable in two of six fluid samples. Active metabolites were also detected in amniotic fluid—nine of 12 norfluoxetine samples, four of six desmethylsertraline samples, and four of four *O*-desmethylvenlafaxine samples.

Analysis of paired amniotic fluid and maternal serum concentrations excluded women with serum collection more than 2 weeks from the time of amniocentesis (subjects J and Y). In the remaining 25 women, the ratio of amniotic fluid to maternal serum concentrations for the parent compound and the metabolite was calculated. The amniotic fluid to maternal serum ratio for the different parent compounds and the metabolites varied from 1.4% to 267.2% for the parent compound and 0.8% to 446.7% for the active metabolites. The maternal serum and amniotic fluid concentrations and ratios for the individual medications are shown in Table 1 (online only).

Obstetrical outcome data were available for all of the 28 infants (27 women and one set of twins). Obstetrical complications included 1) nine of 28 who were preterm deliveries (i.e., <37 weeks gestational age), 2) six of 28 infants who were admitted to a special care nursery, and 3) one of 28 infants who had a low birthweight (i.e., <2.5 kg). The majority of infants (27 of 28) left the hospital with their mothers. Obstetrical outcome data, although important, must be reviewed in the context of the subject group (e.g., advanced maternal age, obstetrical issues warranting fetal lung maturity assessment). The women undergoing third-trimester amniocentesis (subjects D, S, Z, and AA) accounted for three of the nine cases of preterm delivery.

Discussion

Antidepressant pharmacotherapy during pregnancy is clouded by the unknown impact of the medication on the fetus. Fetal antidepressant exposure can be more clearly defined by an improved understanding of the routes of fetal exposure and the factors that influence such pathways. For example, the amniotic fluid concentration of fluoxetine (mean=22.8 ng/ml, SD=17.7) and venlafaxine (mean=71.5 ng/ml, SD=68.2) would increase fetal oral ingestion by a modest 0.02 mg/day and 0.05 mg/day, respectively, during late gestation when the fetus swallows up to 760 ml amniotic fluid per day. The significance of respiratory exposure to antidepressants in the fetus is unknown but can theoretically be both significant and efficient and would bypass fetal hepatic metabolism before CNS exposure. The individual variability and limited group size for particular medications (citalopram, escitalopram, fluvoxamine, paroxetine, and venlafaxine) preclude definitive conclusions. These preliminary results suggest that higher protein binding may be associated with lower amniotic fluid concentrations, although additional study is warranted.

The ratio of the metabolite to parent drug concentration in either maternal serum or amniotic fluid reflects the relative exposure to circulating antidepressant or its major metabolite. A ratio of 1.0 means equal circulating concentrations at the time of sampling. A difference in the ratio between maternal serum or amniotic fluid would reflect a change in the overall exposure to parent drug or metabolite between these two body compartments. These data do not demonstrate any consistent pattern during comparisons of metabolite to parent ratio between maternal serum and amniotic fluid across different patients. The amniotic fluid to maternal serum ratio for norfluoxetine was less than the parent compound ratio in six of 12 cases. Similarly, the amniotic fluid to maternal serum ratios for desmethylsertraline and *O*-desmethylvenlafaxine were less than the parent ratio: two of six and one of three, respectively. The significance of this observation is obscure. It is plausible that the metabolites, by definition more polar than the parent compounds, are less likely to be filtered into amniotic fluid. It also raises a potential concern over the fetal capacity to metabolize antidepressants because of the contribution of fetal urine to the amniotic fluid sample. The impact of pharmacogenetic differences between the mother and fetus on such results remains unexplored. From the clinical perspective, such issues are of concern when we administer medications with active metabolites or metabolites that are potentially toxic (e.g., the *cis* metabolite of nortriptyline).

In the present study, no significant correlation was found between the concentrations of parent compound and/or metabolites in maternal serum and amniotic fluid. This lack of correlation suggests that a more complex set of variables may be involved in determining fetal exposure to antidepressant medications, such as placental and fetal

metabolic capability. Overall, these data reflect the large variability in the factors that control not only the absolute exposure of the fetus to drug and metabolite in amniotic fluid but also the relative exposure to drug or active metabolite in comparison to the more readily available maternal serum from which blood samples can be drawn. Regardless of the contribution of maternal and fetal hepatic elimination of antidepressants, these data suggest that fetal development occurs in a continuous environment of pharmacologically active drug molecules when mothers are treated with these medications.

These amniotic fluid antidepressant concentration results provide a means by which physicians might better quantify and ultimately limit fetal antidepressant exposure. Collectively, data obtained on placental passage (5, 7), appearance in amniotic fluid (5), breast milk excretion (8–10), and CNS quantification in laboratory animal models (11) may elucidate the pharmacological and physiological determinants of fetal and neonatal antidepressant exposure. Such factors could stimulate development of novel pharmaceutical agents that less readily enter amniotic fluid, fetal circulation, and breast milk and would therefore be preferable for women of childbearing age.

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See the online version of this article for supplemental data.

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