Antenatal Exposure to Selective Serotonin Reuptake Inhibitors and Duration of Gestation

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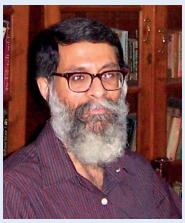

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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Clinical Question

Some studies suggest that the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy increases the risk of preterm delivery. If so, to what extent is this a matter of clinical concern, and how should the subject be discussed with patients?

SSRIs and Preterm Delivery

Some,[1–10] but not all,[11–17] studies suggest that the use of SSRIs during pregnancy increases the risk of preterm delivery; in the positive studies, the risk appears to be approximately doubled, on average, in SSRI-exposed relative to unexposed women. An important limitation of these studies is that all were observational in design. In such studies, there is no way of knowing whether the adverse outcome is due to the drug that was used or to the indication for which the drug was prescribed; in other words, maternal depression and the severity thereof (and behaviors and experiences related thereto), rather than SSRI use, could have explained the increased risk of preterm delivery in SSRI-treated pregnant women.

In one study[6] that compared SSRI-treated women with untreated depressed controls, there was no increase in risk. In the only study to date that described propensity-matching as a method to control for the presence and severity of maternal depression, Oberlander et al[18] found that both the duration of gestation and the risk of preterm delivery did not differ significantly between depressed women who had used SSRIs during pregnancy and those who had not.

Most studies calculated odds ratios (ORs) to estimate the risk of preterm birth associated with SSRI use. This approach is useful for 2 reasons: preterm birth is an important categorical outcome, and calculating ORs allows for the adjustment for potential confounding variables such as maternal age, socioeconomic status, physical illness, smoking, and alcohol use. In the case of an actual patient, however, what could be more important is an estimate of the absolute degree of earlier birth, expressed in days, regardless of correction for confounds. This article will therefore focus on the implications of absolute estimates.

Absolute Estimate of Difference in the Duration of Gestation

Few papers that found an increased risk of SSRI-associated preterm delivery presented absolute estimates. When these data were available and the difference was statistically significant, the degree of earlier birth associated with SSRI exposure (relative to SSRI-unexposed women, regardless of presence of depression) was in the region of 2–6 days,[3,5,7,8,16,18] with most studies finding smaller rather than greater differences. In a systematic review and meta-analysis of 15 studies, Ross et al[19] found that gestational age was 3.2 (95% CI, 1.8–4.5) days shorter in women exposed to antidepressants relative to women in control groups; there was little difference in analyses restricted to different sets of controls.

So, the question that faces the reader is, "How serious a matter is it for a baby to be born 2–6 days earlier?" This article examines recent literature on the subject.

- Some, but not all, studies suggest that selective serotonin reuptake inhibitor (SSRI) use during late pregnancy increases the risk of preterm delivery. Even if this is so, we cannot yet say whether the risk is related to SSRI treatment or to the depression (and its correlates) for which the SSRIs were prescribed.
- In studies that found significant differences, the duration of gestation was shorter by 2–6 days in women who received SSRIs during pregnancy relative to women who did not.
- A recent large randomized controlled trial found no differences in maternal and neonatal outcomes between deliveries conducted during week 38 and week 39 of gestation. This implies that even if SSRIs do anticipate delivery by a few days, it may not matter much.

Table 1. Neonatal Outcomes After Elective Cesarean Section During Week 38 vs Week 39 of Gestation[a]

In the week 38 group, there were 88/635 (13.9%) NICU admissions within 2 days of birth; this rate was 76/637 (11.9%) in the week 39 group (RR = 0.86; 95% CI, 0.65–1.15)
Week 39 neonates were significantly less likely to require treatment with continuous oxygen for more than 1 day (RR = 0.31; 95% CI, 0.10–0.94). This finding, however, was no longer significant after correction for multiple comparison testing
Week 39 mothers were significantly less likely to experience bleeding of > 500 mL (RR = 0.79; 95% CI, 0.63–0.99). This finding, too, was no longer significant after correcting for multiple comparisons
The 2 groups did not differ significantly in other outcomes such as the frequency of NICU admission within 7 days of birth, NICU stay for > 2 days, neonatal respiratory morbidity, and neonatal treatment with intravenous antibiotics. A maternal composite outcome also did not differ significantly between the 2 groups (RR = 1.1; 95% CI, 0.79–1.53)

[a]Data from Glavind et al.[25]
Abbreviations: NICU = neonatal intensive care unit, RR = risk ratio.

Defining Term Pregnancy

Babies are ideally born at full term, that is, after 40 weeks of gestation. This is because many disadvantages related to health and development affect babies born preterm and because several problems are associated with postterm birth, as well.[20]

The onset of gestation is conventionally defined as the first day of the last menstrual period. With this date as the reference, *preterm* and *postterm births* are conventionally defined as birth before 37 weeks and birth after 42 weeks of gestation, respectively. In line with convention, *term pregnancy* in *ICD-10* is defined as delivery between 37 weeks 0 days and 41 weeks 6 days of gestation.[20]

Babies born between 34 weeks 0 days and 36 weeks 6 days of gestation were formerly considered to be near term. In 2005, a US National Institute of Child Health and Human Development workshop suggested that "near term" be replaced by "late preterm" because the health disadvantages suffered by babies born during this period are more similar to those of preterm babies than those of term babies.[20]

Fetal maturation does not stop at week 37, and the period constituting term spans 5 weeks. It is therefore logical to expect that outcomes could vary depending on when delivery occurs during term pregnancies. In line with these expectations, observational data show that the best maternal and neonatal outcomes are associated with birth between 39 weeks 0 days and 40 weeks 6 days.[21–24]

To reduce heterogeneity of outcomes and to bring greater precision into the field, the National Institute of Child Health and Human Development, the American Congress of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Society for Maternal-Fetal Medicine, the March of Dimes, and the World Health Organization participated in a workshop in December 2012.[20] The recommendations of the workshop are summarized below:

- Births occurring between 37 weeks 0 days and 38 weeks 6 days should be designated as early term.
- Births occurring between 39 weeks 0 days and 40 weeks 6 days should be considered as full term.
- Births occurring between 41 weeks 0 days and 41 weeks 6 days should be designated as late term.

Spong[20] observed that the new terminology has obvious implications for counseling, management, and research. What might be the implications for SSRI-exposed pregnancies?

Week 38 vs Week 39

The reclassification presented above describes splits that are 2 weeks in duration; what about splits that are narrower, such as a week in duration? After all, the average decrease in gestation duration after antenatal SSRI exposure was in the region of a few days, at the most, in the studies that did find differences between SSRI-exposed and unexposed pregnancies. A new study[25] provides some interesting insights in this regard.

The authors[25] describe a Danish, 7-center, open-label, randomized controlled trial (RCT) of perinatal outcomes after elective cesarean section that was scheduled at a gestational age of either 38 weeks 3 days or 39 weeks 3 days (with a window of 2 days on either side of the target day in each group). The sample included 1,274 women (mean age = 32 years) with uncomplicated, singleton pregnancies. The median difference in gestation duration between groups was 6 days.

The study[25] found no significant differences between the 2 groups in neonatal intensive care unit (NICU) admission within 48 hours of birth, NICU admission within 7 days, NICU length of stay, neonatal respiratory problems, neonatal treatment, or maternal outcomes. The results are summarized in Table 1.

Implications for Use of SSRIs During Pregnancy

The Danish study[25] is important because it is the first RCT in the field; previous studies that examined the relationship

between gestational age and perinatal outcomes were all observational in design. The findings of the Danish study[25] suggest that, if a sample size in excess of 1,200 women was unable to find significant differences in neonatal or maternal outcomes between deliveries during week 38 and week 39 of gestation, then SSRI exposure-related anticipation of delivery by a few days is not likely to make a demonstrable difference. The Clinical Points listed at the beginning of this article summarize the evidence in a way that can be presented to patients. It must be kept in mind, though, that the Danish study[25] examined only perinatal outcomes. We do not as yet know whether the difference of a week in gestational age could result in differences in neurodevelopment or in differences in health and health care utilization during childhood or later.

Parting Note

Precise definitions of *preterm, term,* and *postterm* have little meaning if the starting point (the date of the first day of the last menstrual period) is inaccurately remembered or if it inaccurately reflects fetal age. Spong therefore proposed an algorithm for the determination of gestational age based on the date of the last menstrual period, the results of a sonogram, and other data. Readers may wish to consult this algorithm.[20]

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