Selective Serotonin-Reuptake Inhibitors and Persistent Pulmonary Hypertension of the Newborn

TO THE EDITOR: Several publications have recently reported an association between maternal treatment with selective serotonin-reuptake inhibitors (SSRIs) late in pregnancy and adverse outcomes in infants. These outcomes have included persistent pulmonary hypertension of the newborn (PPHN), as reported by Chambers et al. (Feb. 9 issue),[1] and the neonatal abstinence syndrome, a condition found in infants born with drug dependency.[2] Also, the Food and Drug Administration recently published a public health advisory concerning increased rates of congenital defects (and, specifically, heart defects) after the use of the SSRI paroxetine early in pregnancy.[3] However, little information is available on the frequency of SSRI treatment during pregnancy.[4]

We have obtained such data from the National Birth Defects Prevention Study, a population-based, case–control study of congenital anomalies conducted in eight states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas).[5] Mothers of liveborn infants without birth defects (controls) were randomly selected at each site. Among 4094 control mothers who delivered their infants from October 1997 to December 2002 and completed an hour-long interview on exposures during pregnancy, 113 reported the use of SSRIs within three months before conception and through the end of pregnancy (2.8 percent), including 95 who used SSRIs during pregnancy (2.3 percent). These findings were similar to those regarding the frequency of use of SSRIs during pregnancy in the study by Chambers et al. among the matched controls (2.9 percent).[1]

Figure 1 shows the prevalence of the use of SSRIs (and, specifically, of fluoxetine, sertraline, and paroxetine) and the use of any prescription antidepressant within three months before conception and through the end of pregnancy. The use of the drugs decreased after the first month of pregnancy: of the 76 women who used an SSRI in the first month of pregnancy, 23 discontinued treatment by the second month (30.3 percent). Between 1997 and 2002, there was no significant change in the reported use of SSRIs during pregnancy (1.5 percent of pregnancies in 1997 and 1998, 2.8 percent in 1999 and 2000, and 2.3 percent in 2001 and 2002); the reported use of any prescription antidepressant followed a similar pattern (2.0 percent, 3.3 percent, and 2.6 percent, respectively). Of 151 specific reports of antidepressant use by 140 control mothers before and during pregnancy, most involved SSRIs (77.5 percent), with bupropion (a norepinephrine- and dopamine-reuptake inhibitor) the second most

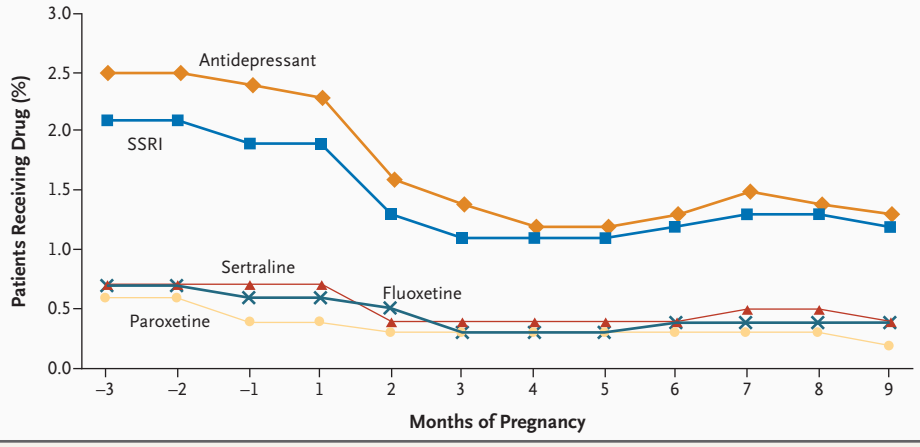

Figure 1. The Use of SSRIs and Other Antidepressant Drugs among 4094 Women from Three Months before Conception through the End of Pregnancy.

Data are from the National Birth Defects Prevention Study, 1997–2002. SSRI denotes selective serotonin-reuptake inhibitor.

commonly used agent (10.6 percent) and tricyclic antidepressants the third most commonly used class of agents (5.3 percent).

Approximately 4 million live births occur in the United States each year, and about 92,000 of these infants are prenatally exposed to SSRIs. Given the concern that has been expressed,[1-3] more research on the fetal effects of maternal treatment with SSRIs during pregnancy is needed to enable pregnant women and their health care providers to make informed decisions about the management of depression.

Jennita Reefhuis, Ph.D.
Sonja A. Rasmussen, M.D.
Centers for Disease Control and Prevention
Atlanta, GA 30333
nzr5@cdc.gov

Jan M. Friedman, M.D., Ph.D.
University of British Columbia
Vancouver, BC V6T 1Z4, Canada

1. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med 2006;354:579-87.
2. Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med 2006;160:173-6.
3. FDA public health advisory: paroxetine. Washington, D.C.: Center for Drug Evaluation and Research, Food and Drug Administration, December 2005. (Accessed April 19, 2006, at http://www.fda.gov/cder/drug/advisory/paroxetine200512.htm.)
4. Mills JL. Depressing observations on the use of selective serotonin-reuptake inhibitors during pregnancy. N Engl J Med 2006;354:636-8.
5. Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. Public Health Rep 2001;116:Suppl 1:32-40.

TO THE EDITOR: We have some concerns with regard to the study by Chambers et al., which concluded that the use of SSRIs in late pregnancy is associated with PPHN. Infants with malformations were excluded from the control group but not from the group with PPHN (cases), except for some cardiac malformations, which leaves a possibility of selection bias with regard to exposure. It is worth noting that none of the controls had been exposed to paroxetine, an SSRI associated with cardiac malformations.[1]

Information on medical history and concomitant medication (except for nonsteroidal anti-inflammatory drugs) was not reported. The authors suggest that confounding by indication was unlikely because non-SSRI antidepressants were not associated with PPHN and because SSRIs were associated with an increased risk of PPHN only when exposure occurred in the second half of pregnancy. However, confounding by indication cannot be excluded since women who require SSRI therapy to term may have had more severe psychiatric illnesses than those who discontinued therapy early. Thus, mothers of case patients could have been more severely ill, with more associated complications and use of medications. These issues warrant consideration in the interpretation of the study results.

Pär Hallberg, M.D., Ph.D.
Viveca Odlind, M.D., Ph.D.
Medical Products Agency
75103 Uppsala, Sweden
par.hallberg@mpa.se

Viktoria Sjöblom, Ph.D.
Uppsala University Hospital
75185 Uppsala, Sweden

1. FDA public health advisory: paroxetine. Washington, D.C.: Center for Drug Evaluation and Research, Food and Drug Administration, December 2005. (Accessed May 1, 2006, at http://www.fda.gov/cder/drug/advisory/paroxetine200512.htm.)

THE AUTHORS REPLY: Dr. Reefhuis and colleagues provide data regarding the prevalence of SSRI exposure that are similar to those we identified among controls (as listed in Table 2 of our article) and also provide important data on the use of SSRIs by women during specific months immediately before and during pregnancy.

We appreciate the questions raised by Dr. Hallberg and colleagues regarding possible alternative explanations for our findings on the use of SSRIs in late pregnancy and PPHN. They suggest that given the putative association of cardiac defects with first-trimester exposure to paroxetine, the inclusion of infants with certain heart defects in the case group could have biased the findings by including more users of paroxetine in this group, thereby creating a spurious association with PPHN. However, none of the four infants with late exposure to paroxetine in the case group had cardiac defects. Dr. Hallberg and colleagues also suggest that confounding by indication cannot be ruled out as an explanation for our findings because women who continued taking an SSRI late in pregnancy might be expected to have more severe underlying disease. However, as can be extrapolated from Table 2 in the article, five mothers in the control group and no mothers in the case group used a non-SSRI anti-

depressant late in pregnancy, indicating no increased risk for PPHN if the antidepressant was not an SSRI. These data argue against confounding by indication as an alternative explanation if exposure to antidepressants in general in late pregnancy represents more severe underlying disease.

Christina Chambers, Ph.D., M.P.H.
University of California, San Diego
La Jolla, CA 92050
chchambers@ucsd.edu
Sonia Hernandez-Diaz, M.D., Dr.P.H.
Allen A. Mitchell, M.D.
Slone Epidemiology Center at Boston University
Boston, MA 02215

Mortality after the Hospitalization of a Spouse

TO THE EDITOR: The study by Christakis and Allison (Feb. 16 issue)[1] has broad implications for our health care system but leaves important questions unanswered. The mortality rates in this study among the elderly persons (referred to as partners) whose husband or wife had been hospitalized were determined according to the first hospital admission of the spouse; multiple admissions of the spouse were not considered in the analysis. These additional admissions may have a substantial impact. Furthermore, the causes of death of the partners are not reported. These deaths may have been preventable. As an example, it is conceivable that partners could share the same high-risk cardiovascular environment that led to the admission of the spouse and the death of the partner from cardiovascular causes. Understanding these factors could influence the future care of partners of hospitalized patients.

Bhavin Patel, B.A.
Amit Parekh, M.D.
Michael D. Ezekowitz, M.D., Ph.D.
Lankenau Institute for Medical Research
Wynnewood, PA 19096

1. Christakis NA, Allison PD. Mortality after the hospitalization of a spouse. N Engl J Med 2006;354:719-30.

TO THE EDITOR: The study by Christakis and Allison underscores the complex connection between marriage and health. However, their use of hospitalization as a marker of caregiver stress among partners residing within the ZIP Codes of the hospitalized spouse involves an immense conceptual leap. Without information regarding spousal cohabitation, care provisions, and the experience of stress, the authors attribute the observed mortality effect largely to mechanisms of caregiver stress. Although we have previously reported on an association between caregiving and mortality,[1] caution is advised in reaching this conclusion on the basis of the data reported in this study.

The finding that husbands fare worse than wives in the face of spousal illness is particularly troubling for an interpretation regarding the stress of caregiving. Caregiving is typically provided by wives, daughters, and daughters-in-law, with husbands infrequently serving as the primary caregiver. Moreover, men who do provide care consistently have lower levels of stress than do women.[2] Taken together, these factors would predict greater mortality for wives than husbands.

Despite these concerns, we applaud the authors' call for interventions to support the partners of inpatients and suggest that chronically ill spouses may be ideal targets of these services.

Jennifer H. Lingler, Ph.D., F.N.P.
Lynn M. Martire, Ph.D.
Richard Schulz, Ph.D.
University of Pittsburgh
Pittsburgh, PA 15260

1. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. JAMA 1999;282:2215-9.
2. Yee JL, Schulz R. Gender differences in psychiatric morbidity among family caregivers: a review and analysis. Gerontologist 2000;40:147-64.

THE AUTHORS REPLY: Our work used the admission of a spouse to a hospital as a marker for the onset of serious spousal disease, and it followed spouses and their partners for long after the hospitalization. No doubt, additional admissions with the same or other diseases could be markers for still worse illness in a spouse that might contribute to additional health problems in partners. However, this fact does not undercut our findings; indeed, our approach can be seen as a kind of intention-to-treat analysis in which we observe the implications of spousal hospitalization regardless of what happens subsequently.

Patel et al. are right to suggest that some deaths among caregiving partners may be preventable. However, the specific causes of death or of any excess mortality were not the focus of our study.