Brief Report

Pregnancy Outcome Following Maternal Use of the New Selective Serotonin Reuptake Inhibitors

A Prospective Controlled Multicenter Study

Nathalie A. Kulin, MSc; Anne Pastuszak, MSc; Suzanne R. Sage, RN, MS; Betsy Schick-Boschetto, MSc; Glenda Spivey, MS, CT; Marcia Feldkamp; Kelly Ormond, MS; Doreen Matsui, MD; Amy K. Stein-Schechman, MS; Lola Cook, MS; Joanne Brochu; Michael Rieder, MD; Gideon Koren, MD

Context.—Although a large number of women of reproductive age use new selective serotonin reuptake inhibitors (SSRIs) and half of all pregnancies are unplanned, no data exist on the safety of these agents for the human fetus.

Objective.—To assess fetal safety and risk of fluvoxamine, paroxetine, and sertraline.

Design.—A prospective, multicenter, controlled cohort study.

Setting.—Nine Teratology Information Service centers in the United States and Canada.

Patients.—All women who were counseled during pregnancy following exposure to a new SSRI and followed up by the participating centers. Controls were randomly selected from women counseled after exposure to nonteratogenic agents.

Main Outcome Measures.—Rates of major congenital malformations.

Results.—A total of 267 women exposed to an SSRI and 267 controls were studied. Exposure to SSRIs was not associated with either increased risk for major malformations (9/222 live births [4.1%] vs 9/235 live births [3.8%] in the controls, relative risk, 1.06; 95% confidence interval, 0.43-2.62) or higher rates of miscarriage, stillbirth, or prematurity. Mean (SD) birth weights among SSRI users (3439 [610] g) were similar to the controls (3445 [610] g) as were the gestational ages (39.4 [1.7] weeks vs 39.4 [1.9] weeks).

Conclusion.—The new SSRIs, fluvoxamine, paroxetine, and sertraline, do not appear to increase the teratogenic risk when used in their recommended doses.

JAMA. 1998;279:609-610

A DECADE after the introduction of the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, into clinical use, this class of antidepressants is being used by millions of men and women worldwide. Because more than half of all pregnancies are unplanned and an estimated 8% to 20% of all women suffer from depression, fetal safety is a primary concern. During the last decade, several studies have reported on pregnancy outcome following first-trimester or whole-pregnancy exposure to fluoxetine. Although there was no evidence of major malformations or behavioral teratology, women who took fluoxetine throughout pregnancy had more perinatal complications and more minor malformations, possibly as a result of risks associated with more severe depression.

During the last few years new SSRIs have been introduced into the market. Currently, while a large number of women of reproductive age use newer SSRIs for depression and other indications (such as obsessive compulsive disorder), no human data on their reproductive safety exist.

Animal teratology studies with fluvoxamine (up to 80 mg/kg per day), paroxetine (up to 43 mg/kg per day), and sertraline (up to 80 mg/kg per day) failed to show an increased risk of fetal dysmorphology or other perinatal complications. Spontaneous reports to the manufacturers are sparse and include both retrospective and prospective cases with no controls, precluding the ability to estimate fetal risk.

We report on the first prospective, controlled, cohort study of pregnancy outcome following fetal exposure to the new SSRIs.

Patients and Methods

This prospective cohort included all women who contacted 1 of 9 participating Teratology Information Service centers regarding exposure to fluvoxamine, paroxetine, and sertraline during the first trimester of pregnancy for depression. Excluded were women who, in addition to being exposed to a new SSRI, were also exposed to a known human teratogen or drugs of uncertain teratogenicity. The group exposed to SSRIs was matched to controls who were randomly selected from the total group of women counseled and followed by the Motherisk Program after exposure to agents proven to be nonteratogenic (eg, dental x-rays, acetylamino-phen).

During the initial interview at the time of exposure, women were asked about a variety of health-related issues including diagnosis; SSRI dose schedule and length of therapy; other drug therapy; recreational drug use; cigarette and alcohol consumption; past medical, obstetric, and genetic history; and exposure to environmental toxins. After the expected date of confinement, women were contacted and interviewed regarding the course of pregnancy, pregnancy outcome, and neonatal health. In most cases, these interviews were conducted 6 to 9 months after delivery. Reports of major malformations were corroborated with medical records.

The primary end point of interest was the rates of major malformations, de-
Controls
Selective Serotonin Reuptake Inhibitors (SSRIs) vs
tween the groups, with similar rates of ma-
neous among the 3 SSRIs (data not shown).

(Table 1). These trends were homoge-
neous among the 3 SSRIs (data not shown).

Pregnancy outcome among women who
took an SSRI throughout pregnancy did not differ from those who took the drug
only during the first trimester. Among
SSRI users, there were no differences in
outcome measures between smokers and
nonsmokers (data not shown).

Comment
Because half of all pregnancies are un-
planned, 3 several months after the intro-
duction of the new SSRIs into clinical use,
our centers were contacted by many
women who found out they had con-
dered while taking fluvoxamine, parox-
etine, or sertraline. Moreover, other
women who have benefited from these
drugs wished to find out, on planning
pregnancy, whether the new SSRIs are
safe for their unborn fetuses.

Typically, women are excluded from
premarketing clinical trials as it is per-
cieved to be medically unethical to test
drugs during human pregnancy. This
results in a lack of fetal safety information
on introduction of the drug into the mar-
et, and the SSRIs are not an exception.

Our study confirms animal ex-
periments by showing that when used in
the recommended doses, the new SSRIs do
not appear to increase the risk of con-
genital malformations. Our sample size
was large enough to detect a relative risk
of 2.5 for major malformations with a
power of 80% and an α of .05. However, the
almost identical rates (222 vs 235) be-
tween the SSRI and control groups
implies that thousands more cases in
those reported in the general population. 11

Our study was not designed to address
potential behavioral teratology of SSRIs. A
recent study with fluoxetine failed to find
differences in IQ, language, and behavior
after fetal exposure to the drug. 4 Recent
findings of more minor malformations and
perinatal complications among infants
exposed to fluoxetine throughout preg-
nancy are difficult to interpret because the
study did not control for depression. 5 When
controlled for depression with a group ex-
exposed to tricyclic antidepressants, infants
exposed to fluoxetine in utero do not ap-
pear to have more minor malformations 6
or perinatal complications (I. Nulman, writ-
ten communication, October 1, 1997).

In summary, this study indicates that
the new SSRIs, fluvoxamine, paroxetine,
and sertraline, do not appear to
increase the teratogenic risk when used
in their recommended doses.

References
2. Kessler RC, McGonagle KA, Swartz M, Blazer DG,
Nelson CB. Sex and depression in the National Com-
3. Pastuszak A, Schick-Boschetto B, Felikmamp, K et
al. Pregnancy outcome following first trimester exposure to
4. Chambers CD, Johnson KA, Dick LM, Felix Ed, Jones
KL. Birth outcomes in pregnant women taking
5. Nulman I, Rovet J, Stewart D, et al. Neurode-
velopment of children exposed in utero to antide-
pressant pharmacotherapy: economic evaluation of
fluoxetine, paroxetine, and sertraline in a health main-
7. Carpenter LL, McDougie DL, Epperson CN, Price
HL. A risk-benefit assessment of drugs used in
the management of obsessive compulsive disor-
8. Luxov [package insert]. Scarborough, Ontario:
SmithKline Beecham Pharmaceuticals; 1995.
10. Zoloft [package insert]. Kirkland, Quebec: Pfizer
Pharmaceuticals; 1994.
11. Koren G, Pellegrini E, MacLeod SM, Motherisk: a
new model for counselling in reproductive toxicology.
In: Koren G, ed. Maternal Fetal Toxicology. A Clinician’s

Table 1.—Maternal Demographics: Exposed to Selective Serotonin Reuptake Inhibitors (SSRIs) vs Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exposed to SSRIs, No. (n=267)</th>
<th>Controls, No. (n=267)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>57</td>
<td>199</td>
<td>.005</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>95</td>
<td>125</td>
<td>.07</td>
</tr>
<tr>
<td>Previous spontaneou abortion</td>
<td>152</td>
<td>142</td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>157</td>
<td>205</td>
<td>.91</td>
</tr>
<tr>
<td>Previous therapeutic abortion</td>
<td>166</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td>≥0</td>
<td>40</td>
<td>31</td>
<td>.03</td>
</tr>
<tr>
<td>Tobacco consumption</td>
<td>Yes</td>
<td>No</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>224</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Yes</td>
<td>No</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>169</td>
<td>.94</td>
</tr>
<tr>
<td>Maternal age at conception, mean (SD)</td>
<td>31.3 (4.7)</td>
<td>30.8 (4.9)</td>
<td>.29</td>
</tr>
</tbody>
</table>

*Mature age was unknown for 4 SSRI cases.

Table 2.—Pregnancy Outcome: Exposed to Selective Serotonin Reuptake Inhibitors (SSRIs) vs Controls

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposed to SSRIs, No.</th>
<th>Controls, No.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live births</td>
<td>222</td>
<td>235</td>
<td>.46</td>
</tr>
<tr>
<td>Spontaneous abortions</td>
<td>30</td>
<td>21</td>
<td>.24</td>
</tr>
<tr>
<td>Therapeutic abortions</td>
<td>15</td>
<td>9</td>
<td>.30</td>
</tr>
<tr>
<td>Stillbirths</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Major malformations</td>
<td>9</td>
<td>9</td>
<td>.91</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>3439 (505)</td>
<td>3445 (610)</td>
<td>.91</td>
</tr>
<tr>
<td>Gestational age, mean (SD), wk</td>
<td>39.4 (1.7)</td>
<td>39.4 (1.9)</td>
<td>.71</td>
</tr>
</tbody>
</table>

Table 3.—Number of Major Malformations in the Selective Serotonin Reuptake Inhibitor (SSRI) and Control Groups

<table>
<thead>
<tr>
<th>Malformation</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double urinary collecting system</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac malformations</td>
<td>2</td>
</tr>
<tr>
<td>Absent corpus callosum</td>
<td>1</td>
</tr>
<tr>
<td>Bilateral club foot</td>
<td>1</td>
</tr>
<tr>
<td>Ear malformation</td>
<td>1</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>1</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>1</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>Cardiac malformations</td>
<td>4</td>
</tr>
<tr>
<td>Inguinal hernia</td>
<td>2</td>
</tr>
<tr>
<td>Undescended testis</td>
<td>1</td>
</tr>
<tr>
<td>Ectopic kidney</td>
<td>1</td>
</tr>
<tr>
<td>Vesicourethral reflex</td>
<td>1</td>
</tr>
</tbody>
</table>