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Louik C, Lin AE, Werler MM, Hernández-Díaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med.* 2007;356:2675–2683.

FAST TRACK

Two studies show that SSRIs are not major teratogens, but more investigation is needed

Q. Do SSRIs cause major birth defects?

A. No. However, these two studies found some evidence that use of selective serotonin-reuptake inhibitors (SSRIs) at the time of conception or during pregnancy is associated with anencephaly, craniosynostosis, and omphalocele—although the absolute risk was very low and the association needs to be confirmed by further study. These studies also found a significant association between specific SSRIs and birth defects, such as paroxetine (Paxil) and right ventricular outflow tract obstruction, but, again, the absolute risk was very low and the birth defects in question are rare.

EXPERT COMMENTARY

Andrew M. Kaunitz, MD, Professor and Associate Chairman, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Jacksonville, Fla. Dr. Kaunitz is a member of the OBG MANAGEMENT Board of Editors.

Because depression is fairly common among women of reproductive age and is often treated with SSRIs, the issue of teratogenicity is important. Earlier investigations suggested that use of these drugs—particularly paroxetine—during early pregnancy increases the risk of heart defects. These two ongoing case-control studies help clarify the relationship between prenatal use of SSRIs and birth defects, although the issue still has not been addressed definitively.

Both studies involved large populations

The first study was conducted by investigators from the Centers for Disease Control and Prevention and the University of British Columbia. It involved

9,622 infants with major birth defects and 4,092 control infants, all of whom were born between 1997 and 2002. Case infants were identified using birth-defect surveillance systems in eight US states, and control infants were randomly selected from the same regions. A woman was considered exposed to an SSRI if she used any of the medications from 1 month before to 3 months after conception.

Investigators found no significant association between maternal SSRI use in early pregnancy and most categories of birth defects, including congenital heart defects. However, they found a significant association between maternal SSRI use and anencephaly (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.1–5.1), craniosynostosis (OR, 2.5; 95% CI, 1.5–4.0), and omphalocele (OR, 2.8; 95% CI, 1.3–5.7). Use of paroxetine correlated with higher pooled ORs for these three birth defects, as well as a significantly increased risk of right ventricular outflow tract obstruction.

The study by Louik and associates was funded by the National Institutes of Health and GlaxoSmithKline, the manufacturer of Paxil. It involved 9,849 infants with major birth defects and 5,860 control infants, all of whom were born in the United States or Canada between 1993 and 2005. All infants in the case and control groups were identified through their participation in the Slone Epidemiology Center Birth Defects Study, a continuing analysis of medication use in pregnancy. Because Louik and colleagues focused on first-trimester use of SSRIs, exposure was defined as use of any SSRI from 28 days before

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TABLE

SSRIs in pregnancy: How they stack up

ANTIDEPRESSANT	ADVANTAGES	DISADVANTAGES*	PREGNANCY CATEGORY
Citalopram (Celexa)	Few interactions with other medications	No behavioral studies in human pregnancy	C
Escitalopram (Lexapro)	Few interactions with other medications	No systematic studies in human pregnancy	C
Fluoxetine (Prozac)	Has been studied in human pregnancy, with data from meta-analysis and neurodevelopmental follow-up	More reports of neonatal side effects than some other antidepressants	C
Paroxetine (Paxil)	None	No behavioral studies in human pregnancy More reports of neonatal side effects than most other antidepressants Association with right ventricular outflow tract obstruction, anencephaly, craniosynostosis, and omphalocele, but absolute risk is small	D; ACOG recommends that this drug be avoided in pregnancy, if possible
Sertraline (Zoloft)	Relatively well studied in human pregnancy Fewer neonatal side effects reported	Possible association with omphalocele and septal defects, but absolute risk is small	C

* ACOG reports that neonates exposed to SSRIs late in the third trimester have developed complications such as jitteriness, mild respiratory distress, transient tachypnea, and poor tone.

Pregnancy category C – Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women, or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.

Pregnancy category D – Has been found to have a harmful effect on fetuses.

Adapted from "Information for Physicians on Prescription Products to Treat Perinatal Depression," University of Illinois at Chicago Perinatal Mental Health Project, August 2007 (www.psych.uic.edu/research/perinatalmentalhealth/).

the last menstrual period through the fourth lunar month (112 days after the last menstrual period).

Use of SSRIs overall was not associated with heart defects, craniosynostosis, or omphalocele, but a significant association was found between paroxetine use and right ventricular outflow tract obstruction (based on 6 exposed subjects) and between septal defects and sertraline use (based on 13 exposed subjects).

Weigh slight risk of defects against risks associated with discontinuation

These studies confirm that SSRIs are

not major teratogens. Nevertheless, any woman planning to conceive and who is worried about using an SSRI during pregnancy should weigh these findings against the risks associated with discontinuing an SSRI during pregnancy.

Heightened surveillance may be justified

Consider second-trimester targeted ultrasonography to rule out fetal anomalies in women who take an SSRI in early pregnancy. And consider psychiatric monitoring for women who discontinue an SSRI before conception or in early pregnancy.

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Q. Does the HPV vaccine benefit all women in the target age range?

A. No. In the FUTURE I trial, among women who were naïve to all strains of the human papillomavirus (HPV) vaccine at the time of inoculation, the vaccine was 100% effective in preventing anogenital lesions, cervical intraepithelial neoplasia (CIN) 2,3, adenocarcinoma in situ, and cervical cancer. In FUTURE II, among the same population, it was 98% effective in preventing all cervical lesions.

However, in FUTURE I, when the groups comprising HPV-naïve and HPV-positive subjects and those with and without preexisting neoplasia were combined, the vaccine was 20% effective in preventing CIN 2,3, adenocarcinoma in situ, and cervical cancer, and 34% effective in preventing genital warts and vulvar and vaginal intraepithelial neoplasia and cancer due to vaccine and nonvaccine HPV types. In FUTURE II, when the same groups were included, the vaccine was 17% effective in preventing all cervical lesions (regardless of the causal HPV type).

The women involved in these trials fell within the target age range for prophylactic vaccination, with ages from 15 to 26 years.

EXPERT COMMENTARY

Neal M. Lonky, MD, MPH, Clinical Professor of Obstetrics and Gynecology, University of California, Irvine, and member, Board of Directors, Southern California Permanente Medical Group.

Even females in the target population for HPV vaccination (ages 9 to 26) present with different histories and risk status. An individual may be a candidate for:

- true primary prevention (no evidence of any HPV subtype or neoplasia)
- primary prevention for the vaccine subtypes (ie, negative for HPV type 6, 11, 16, or 18)
- prevention despite the presence of HPV type 6, 11, 16, or 18
- prevention despite the presence of a subtype not covered in the vaccine

- vaccination despite existing vulvar, vaginal, or cervical neoplasia.

The effect of the vaccine on this last group would be considered both prophylactic and therapeutic, defined as secondary prevention of cervical cancer. Secondary prevention (reversal of HPV effect in CIN lesions, leading to regression) has not been demonstrated with the quadrivalent HPV vaccine (Gardasil).

Trials followed women over 3 years

In these randomized trials, both vaccine efficacy (lesions prevented) and safety (side effects) were evaluated.

FUTURE I enrolled nearly 5,500 young women within the advised age range for prophylaxis who were randomized to the quadrivalent HPV vaccine or placebo. Cervical screening and colposcopic biopsy (if indicated) were conducted at baseline, and HPV status was determined. Investigators studied the effect of prophylactic vaccination in women naïve to the four viral subtypes targeted by the vaccine (6, 11, 16, and 18), as well as women in each of the other groups listed above.

The principal aim of FUTURE I was to provide an “ideal” frequent visit schedule with broader referral to colposcopy and determine whether the vaccine would reduce the combined incidence of anogenital warts, vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VAIN), CIN 1,2,3, and cancer related to HPV subtypes 6, 11, 16, and 18.

FUTURE II involved 12,167 women and a wider visit interval more consistent with clinical practice than FUTURE I. The aim was to determine whether the quadrivalent vaccine would reduce the incidence of CIN 2,3, adenocarcinoma in situ, or invasive carcinoma of the cervix related to HPV subtypes 16 and 18.

In both trials, polymerase chain reaction was used to identify the HPV

Garland SM, Hernandez-Avila M, Wheeler CM, et al, for the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med. 2007;356:1928–1943.

FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med. 2007;356:1915–1927.

FAST TRACK

The observed efficacy of the vaccine declines when HPV-positive and HPV-naïve subjects, and those with and without preexisting neoplasia, are combined

subtype associated with any CIN, adenocarcinoma in situ, or anogenital lesion that was biopsy-proven, and this information was correlated with the patient's HPV status before and after vaccination. The baseline and postvaccination serological status against HPV subtypes was also measured.

Safety is not a concern thus far

There were no adverse events that caused death or withdrawal from the studies. The most common side effect was pain at the injection site, which occurred more frequently among vaccinated women.

Bottom line: Keep screening

The quadrivalent vaccine is not equally effective among all female candidates. I recommend the following:

- Encourage vaccination in very young girls and virgins. The vaccine is most effective in females who have not been exposed to any of the four subtypes targeted.
- A lack of type-specific, clinically available serology or lower genital tract screening in a woman who is already sexually active leaves the clinician in the dark about how to counsel her. Because most women I counsel do not harbor all four subtypes covered by the vaccine and lack anogenital disease, I offer the vaccine to all women in the age range that is indicated.
- Counsel women who are already sexually active and who harbor HPV before vaccination, as well as those who acquire the virus during the vaccination period, that even with inoculation they are susceptible to infection and neoplastic transformation, unlike those naïve to the vaccine-specific subtypes. Efficacy is still substantial, however—near 90% overall.
- If type-specific HPV testing becomes commercially available, counsel women who test positive for one of the four HPV subtypes targeted by the vaccine, as well as those with other HPV subtypes, that they are

susceptible to neoplastic transformation even with the vaccine.

- Advise women who already have CIN, adenocarcinoma in situ, VIN, VAIN, or benign anogenital disease that the vaccine is not therapeutic and will not prevent the natural progression of these lesions toward cancer.
- Remember that few women harbor all four subtypes targeted by the vaccine. The vaccine may provide some marginal benefit to women already being treated for intraepithelial neoplasia, but each patient should be counseled about the potential lack of benefit.
- Be aware that there is clear benefit in the prevention of anogenital disease independent of the oncogenic risks associated with the virus.
- Don't forget the other 13 known oncogenic HPV subtypes and the many more nononcogenic types identified so far. The effect of the vaccine is modestly reduced in women who harbor one or more of those subtypes when compared with its efficacy in uninfected recipients and virgins. Therefore, screening for cervical cancer and lower genital tract lesions should continue despite vaccination.
- In an editorial accompanying the FUTURE I and II trials, Sawaya and Smith-McCune observed that oncogenic HPV strains not targeted by the vaccine were responsible for a large number of CIN 2,3 and adenocarcinoma lesions in the FUTURE II trial.¹ Although there are no concrete data, the editorialists suggest that, as we vaccinate for known strains, existing strains that are not included or new strains that evolve may "fill the niche" and continue to cause incident cases of neoplasia despite vaccination. This is another reason to screen women cytologically or by direct visual or other in-vivo methods to detect neoplasia. ■

Reference

1. Sawaya GF, Smith-McCune KS. HPV vaccination—more answers, more questions. *N Engl J Med.* 2007;356:1991–1993.

FAST TRACK

The quadrivalent HPV vaccine is most effective in women who have not been exposed to any of the four covered viral subtypes