Brief Report

Pregnancy Outcome Following Gestational Exposure to Venlafaxine: A Multicenter Prospective Controlled Study

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Objective: Because there are no studies available on the safety of venlafaxine during pregnancy, the authors' goal in this study was to determine whether venlafaxine increases the risk for major malformations.

Method: Data on 150 women exposed to venlafaxine during pregnancy in seven pregnancy counseling centers were compared with data from studies of pregnant women who 1) received selective serotonin reuptake inhibitor antidepressants (SSRIs) (N=150) and 2) who received nonteratogenic drugs (N=150).

Results: Among the 150 women who were exposed to venlafaxine during pregnancy, 125 had live births, 18 had spontaneous abortions, and seven had therapeutic abortions; two of the babies had major malformations. There were no significant differences between these women and the two comparison groups on any of the measures analyzed.

Conclusions: These results suggest that the use of venlafaxine during pregnancy does not increase the rates of major malformations above the baseline rate of 1%–3%.

(Am J Psychiatry 2001; 158:1728–1730)

To date, to our knowledge there are no studies on the safety of venlafaxine during human pregnancy. In animal studies (rats and rabbits), venlafaxine did not cause malformations in doses 11–12 times the maximum recommended human daily dose (1). The manufacturer of venlafaxine has a number of spontaneous case reports of women exposed to venlafaxine during pregnancy, documenting both birth defects and healthy babies with no specific pattern of defects (2). It is important to recognize the inherent bias of spontaneous reporting to drug companies, as our group commented in a recent report (3), because companies are much more likely to receive reports of adverse birth outcomes than healthy babies.

Data obtained by the U.K. Drug Safety Research Unit (4) revealed known outcomes of the pregnancies of 39 women who took venlafaxine. There were 26 live births, seven spontaneous abortions, and six therapeutic abortions in this group and no reports of malformations.

A substantial number of women of child-bearing age suffer from depression. Coupled with the fact that at least 50% of pregnancies are unplanned (5), the likelihood of depression during pregnancy means that women will use this drug in early pregnancy. We have found that some women may choose to abort a wanted pregnancy because there is no information on the safety of a particular drug (6). In another one of our studies (7), we found that a number of women elected to discontinue needed antidepressants abruptly after their pregnancy was diagnosed because there was no information on the safety of the drugs.

Because of the paucity of information on venlafaxine, we elected to carry out this study to assess its safety or risk potential during pregnancy. Our main objective was to ascertain whether venlafaxine use during pregnancy raised the baseline risk of 1%–3% for major malformations. Secondary outcomes of interest included rates of spontaneous and therapeutic abortions, mean gestational age, and mean birthweight.

Method

The Motherisk Program and the other participating pregnancy counseling centers provide similar services for pregnant and lactating women and their health professionals. Information is given on the safety or risk potential during pregnancy of drugs, chemicals, radiation, and infectious diseases. For the purpose of this study, we ascertained the outcome of the pregnancy of women who had called each service requesting information about the safety of venlafaxine when they were in the first trimester of the pregnancy.

On successful contact, information on each woman's exposure history and pregnancy outcome were obtained, along with other measures of interest, with the aid of a structured questionnaire. The exposure history included medical indication for drug use, dose, and frequency and timing of administration, as well as maternal demographics and obstetrical history. At follow-up, women were questioned regarding the course of their pregnancy, the health of their child, and specific details of their exposure to venlafaxine and any other drugs or exposure to other risk factors during their pregnancy. Outcomes were confirmed by sending a letter to the child's primary care physician to corroborate the mother's information.

The primary outcome of interest was the incidence of major malformations, which are defined by the presence of any anom-

TABLE 1. Pregnancy Outcomes of Depressed Women Given Venlafaxine, Selective Serotonin Reuptake Inhibitors (SSRIs), or Nonteratogenic Drugs During Pregnancy

Variable	Venlafaxine (N=150)		SSRIs (N=150)		Nonteratogenic Drugs (N=150)		Venlafaxine Versus SSRIs		Venlafaxine Versus Nonteratogenic Drugs		Three Groups Compared	
	N	*%*	*N*	*%*	*N*	*%*	χ^2 *(df=1)*	*p*	χ^2 *(df=1)*	*p*	χ^2 *(df=2)*	*p*
Live birth	125	83.3	124	82.7	137	91.3	0.00	1.00	3.65	0.60	5.72	0.06
Spontaneous abortion	18	12.0	16	10.7	11	7.3	0.03	0.90	1.37	0.24	1.93	0.38
Therapeutic abortion	7	4.7	10	6.7	2	1.3	0.25	0.62	1.83	0.18	5.39	0.06
Major malformation[a]	2	1.6	3	2.4	1	0.7		0.99[b]		0.93[b]		0.89[b]
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*					*F (df=2, 446)*	*p*
Gestation age at birth (weeks)	39	2	38	2	39	2					9.40	0.72
Birthweight (g)	3,332	609	3,429	482	3,452	602					1.63	0.34

[a] Odds ratio between venlafaxine and SSRIs=0.66 (95% confidence interval=0.11–3.99); odds ratio between venlafaxine and nonteratogenic drugs=2.21 (95% confidence interval=0.20–24.69).
[b] Fisher's exact test (two-tailed).

aly that has an adverse effect on either the function or the social acceptability of the individual (8). Secondary outcome measures included the rates of spontaneous or therapeutic abortions, live births and stillbirths, gestational age at birth, and birthweight. Exposure was defined as occurring during organogenesis if the drug was consumed between the fourth and 14th week of gestation.

Data from studies of pregnant women (9–14) were used to create two comparison groups; all of the data in the studies were collected in the same fashion. The first comparison group consisted of women suffering from depression who were taking selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, fluvoxamine, and paroxetine) (9, 10). The second comparison group consisted of women who were given nonteratogenic drugs (loperamide, echinacea, sumatriptan, and dextromethorphan) (11–14). Age, smoking status, and alcohol use were compared in all three groups. Most women were followed up between 6 and 12 months after delivering their babies.

Outcomes of interest were compared among groups by using chi-square analysis, Fisher's exact test, and analysis of variance. We received oral consent from each participant after the study was fully explained over the telephone; the study was approved by the Research Ethics Board of The Hospital for Sick Children.

Results

We were able to ascertain the outcomes of 150 pregnancies after exposure to venlafaxine from seven different centers: Toronto (N=99), Farmington, Conn. (N=15), San Diego (N=13), Rome (N=9), Milan, Italy (N=5), London, Ont., Canada (N=5), and Porto Allegre, Brazil (N=4). All of the women used the drug in the first trimester, and 34 used it throughout their pregnancy. There were no significant differences in maternal characteristics among the venlafaxine and comparison groups, although there were more smokers in both the venlafaxine and SSRI groups. However, the difference did not reach statistical significance, and the amount of cigarettes smoked was relatively light; most women reported having cut down to fewer than 10 cigarettes/day during their pregnancy. There were no differences in any outcome measures in smokers compared with nonsmokers, including the rates of spontaneous abortions.

The majority of the women in the venlafaxine group (70% [N=105]) took 75 mg/day of venlafaxine (immediate release form); the rest fell into a wide range of dosing between 37.5 and 300 mg/day.

Among the women who received venlafaxine, there were 125 live births, 18 spontaneous abortions, and seven therapeutic abortions; the mean birthweight of the children in all three groups was 3,332 g (Table 1). Pregnancy outcome did not differ among the three groups, including preterm delivery rates, with the exception of the fact that more spontaneous abortions were reported in the venlafaxine group (this difference did not reach statistical significance) (Table 1). There were two major malformations (hypospadias and neural tube defect with club foot) in the venlafaxine group, three (ventricular septal defect, pyloric stenosis, and absent corpus callosum) in the SSRI group, and one (congenital heart defect) in the nonteratogenic group.

Discussion

To our knowledge, this is the first prospective controlled study examining the effects of venlafaxine use during pregnancy with a large group of women exposed to the drug in the first trimester (N=150). However, this study does not attempt to evaluate the potential neurobehavioral effects of this drug.

The only difference among the venlafaxine group and the two comparison groups was in the rates of spontaneous abortions, which was nonsignificantly higher in both the venlafaxine group (12%) and the group receiving SSRIs (11%) than in the group receiving nonteratogenic drugs (7%) (Table 1). We found nonsignificantly higher rates of spontaneous abortion in women receiving antidepressants in two previous studies (9, 10). In a study of fluoxetine (9), we found spontaneous abortion rates of 14% in women exposed to fluoxetine, 12% in women exposed to tricyclic antidepressants, and 7% in women not exposed to antidepressants. In a later study of SSRIs (10), we found that the rates of spontaneous abortion were 12% among women exposed to SSRIs and 7% among the general Motherisk population. The differences in both studies were not statistically significant, and the rates for both the

fluoxetine and SSRI groups were within the baseline rate of up to 15% for spontaneous abortions in the general population.

To verify whether our findings regarding spontaneous abortion were statistically significant, we combined the results of the two previous studies with those of the current study using a meta-analytical approach. This produced a weighted mean of 12.2% spontaneous abortions (SE=1.4%) in the groups of women who received antidepressants compared with 7.7% (SE=1.1%) in the other groups, with a summary odds ratio of 1.68 (95% confidence interval=1.12–2.51).

These results raise the question of whether there may be a possible association between depression and higher rates of spontaneous abortion, which was one of the reasons why we selected a comparison group of women who were suffering from depression. Smoking has been found to increase the rates of spontaneous abortion (15); however, we did not find higher rates among the smokers in our study, probably because the vast majority of the women who smoked had cut down their cigarette use in pregnancy to fewer than 10 cigarettes/day. Chatenoud et al. (15) reported that smoking more than 10 cigarettes/day increased the rates of spontaneous abortion.

Women who have been diagnosed with depression before becoming pregnant and are being successfully treated with medication should not feel that they automatically have to stop their medications as soon as their pregnancy is confirmed. If they do decide to discontinue the medication, it should be tapered off slowly to avoid abrupt discontinuation syndrome. Failure to treat depression during pregnancy can have serious ramifications for both the mother and the child, probably the most important being inability to carry out maternal duties and difficulty bonding with the child because of depression (16). A recent study (17) also found that depression and anxiety in early pregnancy are associated with a risk for subsequent preeclampsia.

The main limitation of this study is the number of subjects, which is small for statistical purposes in that it has only an 80% power to detect a four-fold increase in the rate of malformations with an alpha of 0.05. Approximately 800 subjects in each group would be required to detect a two-fold risk of relatively common malformations, and thousands of subjects would be required to detect rare defects.

In summary, the results in 150 women exposed to venlafaxine during pregnancy in the first trimester do not suggest that there is a greater risk for major malformations above the baseline rate of 1%–3%. This evidence-based information can be helpful to women and their health professionals when making the decision whether to treat a depression with venlafaxine during pregnancy.

Received Dec. 8, 2000; revised April 9, 2001; accepted May 3, 2001.
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