RESEARCH ARTICLE

To evaluate the effects of antidepressant drugs on pregnancy outcomes in a university hospital of Turkey

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Abstract

Objective: To assess the effects of antidepressant use on pregnancy outcomes.

Methods: The cross-sectional study was conducted at the Department of Pharmacology, Manisa Celal Bayar University, Manisa, Turkey, and comprised pregnant women who were admitted to the Department of Gynaecology between 2008 and 2017 who had been prescribed antidepressant drugs before pregnancy and continued to use them during any week of their respective pregnancies. The women were contacted by telephone after delivery to obtain information about the pregnancy outcomes. Data was analysed using SPSS 23.

Results: There were 183 women with a mean age of 31.3 ± 5.3 years (range: 18-44 years). There were congenital defects in the newborn in 11(7.65%) cases. The most commonly used antidepressant group was selective serotonin reuptake inhibitor 138(75.4%), and escitalopram was the most frequently used drug 46(25.1%). Spontaneous abortion rate was higher with escitalopram than the other antidepressants (p=0.062). Induced abortion rate was significantly higher in multidrug users compared to those on a single drug (p<0.05).

Conclusion: Selective serotonin reuptake inhibitor was found to be the most used class of antidepressants during pregnancy due to the low side effects and teratogenic effects. When antidepressant treatment is necessary during pregnancy, a single drug can be more suitable.

Keywords: Antidepressant, Pregnancy, Spontaneous abortion, Teratogenic effect. (JPMA 71: 281; 2021)

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Introduction

Pregnancy is a fairly sensitive period during which changes in hormonal and biochemical factors are accompanied by psychological changes. Depression is a frequent psychiatric disorder in the general population, and its incidence during pregnancy has been reported to vary between 7.4% and 12.7%.[1,2] When left untreated, depression and anxiety disorder during pregnancy may lead to preterm birth, intrauterine developmental retardation, and an increase in the rate of pregnancy or delivery complications.[3,4] Moreover, discontinuation of antidepressant therapies during pregnancy increases the risk of disease recurrence by 2.6%, and so drug treatments may need to be continued after conception in patients being treated for depression.[5] On the other hand, various studies have suggested that the use of antidepressant drugs during pregnancy is related with poor foetal outcomes, such as premature delivery, congenital malformations, stillbirth, preterm birth, low birthweight (LBW), and pulmonary hypertension (PHTN).[4,6]

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The use of drugs during pregnancy have vital importance in minimising the risk of teratogenic effects by selecting a drug associated with the lowest level of risk both for the health of the mother and the foetus.[6,7] Among the available antidepressants, selective serotonin reuptake inhibitors (SSRIs) are in common use during pregnancy,[8,9] and these drugs are generally considered to be safe during pregnancy.[10,11] However some studies have shown that paroxetine use during the first trimester of pregnancy was increasing the risk of cardiac defects.[12]

Although studies have been limited in a number of cases, neither an increased risk nor an association with any specific malformation has been found. Serotonin/noradrenalin reuptake inhibitors (SNRIs), selective noradrenalin reuptake inhibitors (NRIs), tetracyclic antidepressants (TCAs) and tricyclic antidepressants (TSAs) constitute the other most commonly used antidepressant drug classes,[10,13] although as their use is less common in daily practice, there is only limited amount of data on their safety during pregnancy and their teratogenic effects.

The current study was planned to evaluate the risk of complications, such as spontaneous abortion, induced abortion or teratogenic effect, in pregnant women who

were using antidepressant medications at any week of pregnancy.

Subjects and Methods

The cross-sectional study was conducted at the Department of Pharmacology, Manisa Celal Bayar University, Manisa, Turkey, and comprised pregnant women who were admitted between 2008 and 2017 who had been prescribed antidepressant drugs before pregnancy and continued to use them during any week of their respective pregnancies. All subjects were referred by Department of Gynaecology. After approval from the institutional ethics review committee, detailed demographic data on the pregnant women was collected and the participants were contacted by telephone after delivery to obtain information about pregnancy outcomes, any history of spontaneous or induced abortion (termination), delivery method and information regarding their infants. Any congenital and structural abnormalities detected in the infants after birth were classified according to the scale devised by Merks et al.[14]

Data was analysed using SPSS 23. Categorical variables were compared using chi-square test or Fisher's exact test, as appropriate. P<0.05 was considered statistically significant.

Results

There were 183 women with a mean age of 31.3 ± 5.3 years (range: 18-44 years). There were congenital defects in the newborn in 11(7.65%) cases. The media time of getting in touch with the Department of Pharmacology for medication was week 7 (interquartile range [IQR]: 4-26 weeks). Overall, 16(8.7%) pregnancies resulted out of consanguineous marriages. Among the subjects, 50(27.3%) were smokers, and 4(2.2%) were consuming alcohol (Table-1). The most common indication for drug use was mood disorders 94(49.7%), followed by depression accompanying a physical condition 63(33.3%), anxiety disorders 25(13.2%) and obsessive compulsive disorder (OCD) 7(3.7%).

The most commonly used drug group was SSRIs 138(75.4%) whereas the most commonly used drug was escitalopram 46(25.1%). The drug group was followed by SNRIs 49(26.8%) TCAs 13(7.1%) and TSAs 8(4.37%). Malformations were reported in 11(7.7%) foetuses. Among them were cardiac malformation, congenital hip dislocation, unilateral renal agenesis, autism, strabismus, umbilical hernia, unilateral renal agenesis, renal and uterine cysts, autism, attention deficit / hyperactivity disorder (ADHD) and patent ductus arteriosus (PDA).

Table-1: Sociodemographic, maternal and obstetric characteristics.

Variable (n=183)	Descriptives n (%) or mean ± S.D.
Age	18-44
Min- Max	31.3 ± 5.3
<35	122 (66.7)
≥35	61 (33.3)
Consanguineous marriage	
Negative	167 (91.3)
Positive	16 (8.7)
Weeks at first contact	
Min.	4
Max.	26
Median	7
Alcohol use	
No	179 (97.8)
Yes	4 (2.2)
Smoking	
No	133 (72.7)
≤5	16 (8.7)
>5	34 (18.6)
Previous pregnancy	
1	27 (14.8)
2	49 (26.8)
≥3	107(58.5)
Previous parity	
0	31 (16.9)
1	68 (37.2)
≥2	84 (45.9)
Spontaneous Abortion	
0	148 (80.9)
1	28 (15.3)
≥2	7 (3.8)
Previous induced abortion	
0	143 (78.1)
1	26 (14.2)
≥2	14 (7.7)

SD: Standard deviation.

There were a total of 215 exposures in 183 pregnancies as 32(17.5 %) patients were exposed to multiple drugs (Table-2).

The rate of induced abortions was higher in those with multiple drug exposure compared to those using single drug (p=0.0056) (Table-3). Spontaneous abortion rate was 12(6.6%) and the induced abortion rate was 43(23.5%). No significant difference was found between the drug groups for major malformation and spontaneous abortion, but spontaneous abortion rate was higher with escitalopram than the other antidepressant drugs (p=0.062). the induced abortion rate was higher with duloksetine 7(33.3%) (p=0.042) and mirtazapine 5(38.4%) (p=0.039).

Table-2: Drug exposures and pregnancy outcomes.

SSRIs	138 (75.4)	9 (6.5)	22 (15.9)	11 (7.7)
Citalopram	6 (3.3)	Nil	2 (4.7)	Nil
Escitalopram	46 (25.1)	a 5 (10.9)	8 (17.4)	2 (4.5)
Fluoxetine	16 (8.7)	1 (6.3)	2 (12.5)	2 (12.5)
Fluvoxamine	3 (1.6)	1 (33.3)	Nil	Nil
Paroxetine	30 (16.4)	1 (3.3)	5 (16.7)	4 (13.3)
Sertraline	37 (20.2)	1 (2.7)	7 (18.9)	3 (8.1)
SNRIs	49 (26.8)	2 (4.1)	12 (24.5)	2 (4.1)
Venlafaxine	26 (14.2)	1 (3.9)	5 (19.2)	1 (3.9)
Milnacipram	2 (1.1)	Nil	Nil	Nil
Duloxetine	21 (11.5)	1 (4.8)	b 7 (33.3)	1 (4.76)
5-HT2 Antagonists	3 (1,6)	Nil	Nil	1 (33.3)
Trazodone	3 (1.6)	Nil	Nil	1 (33,3)
TSA	8 (4.4)	Nil	2 (25.0)	Nil
Amitriptiline	3 (1.6)	Nil	1 (33.3)	Nil
Clomipramine	5 (2.7)	Nil	1 (33.3)	Nil
Tetracyclics	13 (7.1)	1 (7.7)	5 (38.5)	Nil
Mirtazapine	13 (7.1)	1 (7.7)	c 5 (38.5)	Nil
Others	4 (2.2)	Nil	2 (50.0)	Nil
Agomelatine	1 (0.6)	Nil	1 (100)	Nil
Vortioxetine	2 (1.1)	Nil	1 (50.0)	Nil
Opipramol	1 (0.6)	Nil	Nil	Nil
Total	215*	12 (6.6)	43 (23.5)	14 (7.7)

*215 exposures in 183 pregnancies;
a: Spontaneous abortus with escitalopram (p=0.062)
b: Induced abortus with duloxetine (p=0.042)
c: Induced abortus with mirtazapine (p=0.039)
ADHD: Attention deficit hyperactivity disorder
SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin/noradrenalin reuptake inhibitors; TSA: Tricyclic antidepressants; 5-HT2: 5-hydroxytryptamine-2.

Table-3: The relationship between induced abortions and multiple drug use.

	Induced Abortion n (%)		
Multiple drug use	Yes	No	P value
Yes	11 (34.4)	21 (65.6)	0.0056
No	21 (13.9)	130 (86.1)	
Total	32 (17.5)	151 (82.5)	

*Chi Sq= 7.67; DF=1;

Discussion

There have been several studies reporting a high frequency of antidepressant drug use during pregnancy.[8,10-12] SSRIs and SNRIs are antidepressant medications used for the treatment of psychiatric disorders, such as panic-related disorders and obsessive compulsive disorder (OCD), and for physical diseases progressing with a depressive symptomatology, and, as such, are among the most commonly used medications during pregnancy.[9,11,12] A study in Manisa and Trabzon provinces in Turkey reported that antidepressants were the most commonly used drugs in pregnant women.[15] Based on the results of the current study, birth defect rate was 7.7% but incidences of basal malformations in pregnancy vary between 3% and 6%,[10] which develop mainly as a result of genetic causes, and the frequency of malformations reported in the present study was higher than the above-mentioned range. All drugs reported to be associated with teratogenic effects were found to be used during the first trimester of pregnancy in the present study, in which the most commonly reported teratogenic effects were cardiac malformations, which were noted in infants of mothers who used paroxetine and venlafaxine during pregnancy. Other identified malformations included umbilical hernias, autism, PDA, microcephaly, congenital hip fractures, unilateral renal agenesis, strabismus, and uterus and renal cysts, and the medications used in all these cases were in the SSRI and SNRI classes, which are the two most commonly prescribed classes of antidepressants during pregnancy.

The current results indicated that the most commonly used class of antidepressant drugs was SSRIs, and escitalopram was the most frequently prescribed drug within this group. In the SNRI group, venlafaxine and duloxetine, and the TCA mirtazapine were other drugs commonly prescribed during pregnancy. Consistent with our findings, previous studies reported that SSRIs were the first-line pharmacotherapy to treat depression during pregnancy, but an increase in the usage of other antidepressants, such as SNRIs and TCAs, has also been reported.[16,17]

In terms of teratogenic effects, SSRIs are considered to be safe during pregnancy, with several studies reporting no significant increase in the frequency of congenital abnormalities in the infants of mothers who used the SSRI class antidepressants during pregnancy compared to those who did not use it.[8,10,11] A recent study compared 3276 women who had been exposed to TSAa or SSRIs during the first trimester pregnancy with 6617 pregnant women with no exposure, and concluded that there was no increase in the frequency of malformation among women exposed to TSA or SSRI antidepressants during pregnancy.[17] On the other hand, recent studies have suggested that exposure to antidepressants, particularly during the first trimester of pregnancy, may increase the risk of such malformations as omphalocoele, craniocynostosis and congenital heart defects.[18-20] The use of paroxetine during the first trimester of pregnancy was associated with an increased risk of foetal cardiac malformation, and it was therefore recommended to avoid paroxetine use during pregnancy.[20,21] There have also been various studies suggesting that other drugs in the SSRI class, such as sertraline, fluoxetine and

citalopram, may also increase the risk of foetal cardiac defects.[19-21] Although previous studies have provided conflicting results, the general consensus is that the use of SSRI antidepressants during pregnancy is not associated with a statistically significant increase in the risk of foetal malformations.[10,11,17,22-24]

According to the current study, miscarriage rate was higher in escitalopram (42%) compared to other SSRIs and SNRIs in borderline significance limits (p=0.062). This finding is consistent with a study[25] which reported 30% rate in the first 6 weeks of gestation. Of the 5 patients who had miscarriage in the current study using escitalopram, 4 were aged >35 years and 3 of them were using combined antidepressant therapy. This can be considered a factor behind spontaneous abortion.

Although data regarding the SNRI class of antidepressants is more limited in literature, there have been reports suggesting that first-trimester exposure to venlafaxine and duloxetine is not associated with an increased risk of major malformations.[23] In contrast, the current study observed cardiac malformations in two cases using venlafaxine and duloxetine in the first trimester. We did not find any significant associations between maternal characteristics and adverse outcomes. TSAs are less frequently used for the treatment of depressive disorders, and their use during pregnancy is quite rare so there have been no recent studies investigating their teratogenic effects.[24] In the present study, the rate of TSA use during pregnancy was also very low.

One of the most important finding of this study is higher elective abortion rates in multiple drug users compared to single drug use. There was no evidence of foetal abnormality in these cases, and most elective terminations were performed because of personal reasons. Another important finding of the study is the statistically significant high induced abortion rates in women exposed to duloxetine and mitrazapine. A recent study also reported a tendency to elective termination among pregnant women using any type of antidepressants.[25]

Still, as a result of the shortage of studies investigating the teratogenic effects of antidepressants during pregnancy, and the conflicting results reported by previous studies, there is a lack of clear information on the harmful effects of these drugs on a developing foetus.

Although SSRIs and SNRIs may not cause significant unwanted effects, escitalopram and duloxetine should be used with caution among pregnant women. The current, despite its limited sample size, may serve as a hypothesis-generating research for future projects that may focus on the adverse effects of escitalopram, duloxetine and combination therapies of SSRI and SNRI in pregnant women.

Conclusion

The use of mirtazapine, duloxetine and multiple drug use significantly increased the likelihood of induced abortion. Foetal malformation rate was high at 7.7% among antidepressant users. Besides, spontaneous abortion rate was higher in escitalopram users than those of other antidepressant users even though the difference was not statistically significant.

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