Original Paper

DOI: 10.5455/bcp.20160207082039

Safety of Psychotropic Medications in Pregnancy: An Observational Cohort Study

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ABSTRACT:

Safety of psychotropic medications in pregnancy: an observational cohort study

Objective: The question of harmfulness of the psychiatric drugs creates a major dilemma for pregnant women. The risks associated with prenatal psychotropic drug exposure are often overestimated. It is unclear that psychotropic medication or disorders themselves increase the risk of adverse pregnancy outcomes. The purpose of this study is to generate data about the safety of psychotropic drugs in pregnancy and maternal characteristics of the pregnant women exposed to these drugs.

Method: An observational cohort study was performed. Pregnancy outcomes of 135 pregnancies after psychotropic drug exposure are compared to a control group of 275 pregnancies.

Results: There were no statistically significant differences in rates of major malformations, miscarriages, and preterm deliveries between the two groups. However, the rate of elective abortions was higher in the exposed group compared to the control group (11.1% vs. 5.1%, respectively; RR 2.18; 95% CI: 1.09-4.39), and most of them were nulliparous (45.2%). The majority of the pregnant women did not smoke cigarettes and no alcohol consumption was reported in both groups.

Conclusion: Our study showed that there was a tendency to terminate pregnancy among women exposed to psychotropic drugs. An accurate risk assessment about drug safety and informing pregnant women would help to prevent unnecessary terminations of pregnancies.

Keywords: pregnancy, psychotropic medication, drug safety, elective termination of pregnancy, birth defects

Klinik Psikofarmakoloji Bulteni - Bulletin of Clinical Psychopharmacology 2016;26(3):229-37

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Date of submission:
October 30, 2015

Date of acceptance:
February 07, 2016

Declaration of interest:
Z.O., E.O., T.G., S.G., K.V.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Psychiatric disorders are highly prevalent in women of reproductive age. These may first appear during pregnancy and continue to be a problem after pregnancy. In women with pre-existing conditions, pregnancy can also cause worsening of symptoms significantly[1]. Maternal psychological distress is important because of negative effects on fetal development. Although no direct neural connections exist between the mother and the fetus, there is scientific evidence to suggest that psychiatric disorders during pregnancy are associated with poor obstetric outcomes[2].

Treating pregnant women who experience psychiatric illness is often crucial. There are no psychotropic drugs that are considered completely safe to take during pregnancy. Psychotropic drugs that affect the central nervous system can be divided into four main groups: antipsychotics, anxiolytics, antidepressants, and mood stabilizers including anticonvulsants. In the light of current

data, typical antipsychotics and tricyclic antidepressants are accepted as relatively safe in pregnancy. On the other hand, mood stabilizers such as lithium and anticonvulsants are associated with fetal and neonatal complications[3]. Despite safety concerns, a useful psychotropic medication should not be changed in pregnancy if the patient is stable. Abrupt discontinuation of these drugs may trigger or worsen the psychiatric symptoms[4].

Antidepressants, including serotonin reuptake inhibitors (SSRIs) appear to be safe in pregnancy. Several studies have analyzed the relationship between SSRIs and congenital malformations. The use of paroxetine during pregnancy has been associated with a small absolute increase in congenital heart defects[5]; however, results across several other observational studies are inconsistent[6]. Although significant association between exposure to SSRIs and both persistent pulmonary hypertension of the newborn and a self-limiting neonatal behavioral syndrome have been reported in recent studies and meta-analyses, most studies indicate that SSRIs are not major teratogens and not associated with birth defects[7,8].

Exposure to antipsychotics in pregnancy has been associated with increased gestational weight, preterm birth, and gestational diabetes[9]. Most studies on pregnancy outcomes following exposure to the antipsychotics did not reveal any significantly increased risks for malformations[10]. However, conclusions regarding atypical antipsychotics are limited. The use of atypical antipsychotics in polypharmacotherapy has been associated with adverse pregnancy outcomes for both the mother and the child[11]. A recent meta-analysis showed that the use of atypical antipsychotics during the first trimester of pregnancy was associated with a significant increased risk for preterm births and birth defects; however, no specific patterns of congenital malformations were found[12].

Antiepileptic drugs that are used to treat both epilepsy and psychiatric disorders may also cause fetal abnormalities. The highest risk is in women exposed to valproate in pregnancy, and it can be difficult to change medication before or during pregnancy[13]. Antiepileptic drugs should not to be used for other indications than epilepsy in pregnancy. Benzodiazepines are the drugs of choice for the treatment of anxiety in pregnancy when strictly necessary. Use of benzodiazepines in late third trimester and exposure during labor may cause the neonatal withdrawal symptoms[14].

All psychotropic drugs cross the placenta and can be found in amniotic fluid and fetal tissues. The lowest effective dose should be used for the patient in order to minimize prenatal drug exposure. Because of possible side effects of medication and risks to fetus, a well-grounded risk assessment should be conducted. Further epidemiologic studies are needed to better understand and manage the risks since there are limited findings associated psychotropic medication in pregnancy and some inconsistencies. In this observational cohort study, we evaluated the association between prenatal psychotropic drug exposure and the risk of adverse fetal outcome among pregnant women.

METHODS

Participants and study protocol

We collected and evaluated pregnancy outcomes of the women referred to our prenatal consultation service for psychotropic drug exposure between 2007-2012. All contacts to our service were initiated via gynecologists. This observational study was approved by the Clinical Research Ethics Committee of the Celal Bayar University, Turkey (No: 20.478.486.210). All patients were informed that their medical information would be used for scientific research. Written informed consents were obtained from all participants.

Procedure

At the first contact, a detailed patient history form was used to record the following information: maternal demographic data and obstetric history, consanguineous marriage, smoking and alcohol consumption, X-ray and all drug exposures (dose,

duration and timing in pregnancy). Weeks of pregnancy were defined by last menstrual period (LMP). After counseling about the risk of drug exposure, the women and their babies were followed up during a 2-year period. Each newborn baby was checked at birth for signs of problems or complications.

In this study, major congenital and structural abnormalities in infants were primarily examined and classified according to Merks and colleagues[15]. Additionally, we collected data of live births, miscarriages, stillbirths, preterm births and compared to controls that were selected from the non-teratogen exposed pregnancies in the same year applying the same procedure for data collection and follow-up.

Statistical Analyses

The results were expressed as number and percentages. For calculating rates of miscarriages, elective terminations of pregnancy (ETOP) were excluded (number of miscarriages/number of exposed pregnancies, ETOP excluded). Risk ratios with 95% confidence intervals were calculated with the use of SPSS 16.0. For the comparison of continuous variables, Kruskal-Wallis and Mann-Whitney U-tests were used. Proportions were compared using the chi-square test or Fisher's exact test, as appropriate. The results were considered statistically significant when p-values were <0.05.

RESULTS

A total of 135 pregnant women exposed to psychotropic drugs in pregnancy were enrolled in this study. There were no patients lost to follow up. The control group consisted of 275 pregnant women not exposed to known teratogens. The maternal characteristics of the women in the drug-exposed and the control groups are presented in Table 1. The rate of nulliparity was higher in

Table 1: Maternal characteristics and obstetric histories

	Psychotropic drugs (n=135)	Controls (n=275)
Maternal age (in years)		
Median age	29	30
Min- max	17 - 42	18 - 44
Smoking		
No	71.8 %	88.3 %
≤5 cigarettes/day	9.7 %	4.4 %
>5 cigarettes/day	18.5 %	7.3 %
Alcohol		
No	100 %	100 %
Previous pregnancies		
0	39.3 %	28.0 %
1-2	23.7 % - 18.5 %	24.4 % - 25.8 %
≥3	18.5 %	21.8 %
Previous parities		
0	45.2 %	31.3 %
1-2	33.3 % - 13.3 %	37.4 % - 17.9 %
≥3	8.2 %	13.4 %
Previous ETOP		
0	83.6 %	83.6 %
1-2	11.9 % - 1.5 %	12.0 % - 1.2 %
≥3	3.0 %	3.2 %
Previous miscarriages		
0	82.1 %	85.9 %
1-2	14.9 % - 1.5 %	12.7 % - 1.4 %
≥3	1.5 %	0
Weeks at first contact		
Median	8	7
Min- max	3 - 27	3 - 35

ETOP: Elective termination of pregnancy

exposed cohort compared with controls (45.2% vs. 31.3%). Exposed women were more often smokers (28.2% vs. 11.7%), and no alcohol intake was reported by pregnant women in both groups. There were no statistically significant differences regarding the other maternal characteristics between study group and controls.

As shown in Table 2, the most commonly used drugs were escitalopram (n=35), sertraline (n=19), paroxetine (n=14), venlafaxine (n=13), and sodium valproate (n=13). There were a total of 179 exposures in 135 pregnancies, because 34 patients were exposed to two or more drugs. Treatment indications (n=135) were major depression (41.8%), anxiety disorder (14.0%), bipolar disorder (12.5%), schizophrenia (11.8%), psychiatric disorders with epilepsy diagnosis (11.1%), and others (8.8%). In 85% of pregnancies, treatment was initiated before pregnancy. Drug exposures took place in 81% during the first trimester, and 11% in all three trimesters. Medical treatments were discontinued in most of recognized pregnancies. Only women taking anticonvulsant drugs were advised to switch to lamotrigine or levetiracetam monotherapy at first consultation.

There were two pregnancies with major congenital defects (without a genetic background) in the exposed (1.7%) and 3 (1.2%) in the control cohort, RR: 1.41 (95% CI: 0.24-8.33; p=0.51). The birth defects in exposed group were bilateral clubfeet, umbilical hernia, persistent ductus arteriosus, and strabismus in one case; inguinal

Table 2: Drug exposures and pregnancy outcomes

Drug	Exposed pregnancies	Live births	ETOP	Miscarriages	Preterm births	Birth defects	Comments
Escitalopram	35	30	3	2	1	-	Fetal deaths in week 8.
Sertraline	19	17	2	-	-	-	
Paroxetine	14	12	2	-	-	2	Bilateral club feet, umbilical hernia, persistent ductus arteriosus, strabismus, inguinal hernia, cleft palate
Venlafaxine	13	11	2	-	-	-	
Sodium Valproate	13	7	4	2	-	-	Fetal deaths in week 12 and 20.
Fluoxetine	10	9	-	1	-	-	Fetal death in week 12.
Carbamazepine	9 (8 women)	8	1	-	1	-	1 twin pregnancy
Lamotrigine	8	7	1	-	1	-	
Quetiapine	8	5	3	-	-	-	
Alprazolam	7	7	-	-	1	-	
Mirtazapine	7	4	2	1	-	-	Fetal death in week 12.
Hydroxyzine	5	5	-	-	-	-	
Olanzapine	5	5	-	-	-	-	
Amitriptyline	4	4	-	-	-	-	
Duloxetine	3	3	-	-	-	-	
Levetiracetam	3	3	-	-	-	-	
Oxcarbazepine	2	2	-	-	-	-	
Phenytoin	2 (1 woman)	2	-	-	-	-	1 twin pregnancy
Gabapentin	2	1	-	1	-	-	Fetal death in week 12.
Citalopram	2	2	-	-	-	-	
Opipramol	2	2	-	-	-	-	
Risperidone	2	2	-	-	-	-	
Clomipramine	1	-	-	1	-	-	Fetal death in week 12.
Trazadone	1	1	-	-	-	-	
Bupropion	1	1	-	-	-	-	
Lithium	1	-	1	-	-	-	
Total	179*						

*179 exposures in 135 pregnancies; ETOP: Elective termination of pregnancy

Table 3: Pregnancy outcome

	Psychotropics, n (%)	Controls, n (%)	Risk ratio (95% CI[a])	Exposed vs. controls p- value
Exposures	179[b]	275		
Pregnancies	135	275		
Live Births	116 (88.1)[c]	246 (89.4)		
Miscarriaged	6/ 120 (4.9)	15/ 261 (5.7)	0.87 (0.35-2.19)	0.76
ETOP[e]	15/ 135 (11.1)	14/ 275 (5.1)	2.18 (1.09-4.39)	0.025
Preterm Births (<37 weeks)	3/ 116 (2.6)	8/ 246 (3.2)	0.79 (0.21-2.94)	0.50
Birth Defects	2/ 116 (1.7)	3/ 246 (1.2)	1.41 (0.24-8.34)	0.51

[a]Confidence Interval, [b]Multiple drug exposure in 34 cases, [c]Including two twin pregnancies, [d]ETOP excluded, [e]Elective termination of pregnancy

hernia and cleft palate in the other case. Atrial septal defect, spina bifida, and hydrocephalus were observed in controls. No statistically significant differences in proportion of birth defects were found (p=0.51). Because of the low number of pregnancies for each drug exposure, we did not calculate 'substance specific risk'. Pregnancy outcomes associated with drug exposures are shown descriptively in Table 2.

The proportion of live births were similar in both groups (88.1% vs. 89.4%). There were also no statistically significant differences in rates of miscarriages, preterm deliveries, and birth defects between the two groups (Table 3). However, the rate of elective abortions was higher in the exposed group (11.1% vs. 5.1%; RR 2.18; 95% CI: 1.09-4.39; p=0.025).

DISCUSSION

We performed an observational cohort study covering 135 pregnant women who had received psychotropic medication during organogenesis period. We did not find any relationships between psychotropic medication in pregnancy and increased risk of adverse fetal outcome. These results are in accordance with two previous national studies, one covered 126 cases who were followed by a Teratology Information and Follow-up Service in Turkey between 1999 and 2004[16]. Furthermore, several studies did not report an increased risk of major congenital malformations for pregnancies exposed to psychotropics[17,18]. In contrast, Danish and Finnish nationwide studies about prenatal antidepressant exposures, and a Swedish study about second-generation antipsychotics suggested potential teratogenic effects of these drugs[19-21]. Drug utilization patterns differ by geography, and country-specific data cannot be reliably extrapolated to other countries[22]. There is insufficient data on the current drug use during pregnancy and associated outcomes in Turkey. Therefore, new sources of drug surveillance data and clinical studies of drug safety with respect to developmental toxicity are urgently needed.

Based on our results, antidepressants were the most used pharmacological treatment in case cohorts, and SSRIs were the most common group of them. Although there is considerable variation in the types of antidepressant prescribed across the different countries, SSRIs are the most used drugs among pregnant women[23]. On the other hand, there is growing but inconclusive evidence that prenatal SSRI exposures may be associated with congenital heart defects[21,24]. Paroxetine was the first SSRI to be associated with occurrence of congenital malformations, but some investigators suggested that paroxetine was the most frequently prescribed drug in this group and it may have biased the findings of the studies that reported the potential teratogenic effect of paroxetine[25]. In our study group, paroxetine was also one of the most used psychotropic drugs (n=14), and we observed major congenital malformations in two cases who have used paroxetine in the first trimester. Both cases with birth defects had some similarities, namely their age, drug-exposure time and obstetric histories. They were multiparous women with paroxetine exposure in the first trimester and previous miscarriage experiences. Although it is

thought previous miscarriages increase the risk of birth defects, we did not find any significant associations between maternal characteristics and adverse outcomes. In this study, all antidepressant exposures were in the first trimester. Clinical course of psychiatric disorders in the patients was not followed up.

Antiepileptic drugs (AEDs) are also psychotropic drugs used to treat both epilepsy and psychiatric disorders. There is a remarkable increase in risk of mood or anxiety disorders and risk of suicide in patients with epilepsy compared with the general population[26]. Because of the prenatal drug exposures and disease itself, infants born to epileptic mothers have an increased risk of birth defects. Classical AEDs, especially valproate and carbamazepine are considered teratogenic. Although many studies among pregnant women indicate that valproate significantly increases the risk of anatomical and behavioral teratogenic effects, the majority of pregnancies in epileptic women exposed to AEDs are uneventful[27]. In our study, we observed 33 women exposed to AEDs in pregnancy. Four of them had multiple antiepileptic drug exposure, and two cases had twin pregnancies. There were no congenital abnormalities noted. Of the 33 pregnancies exposed to AEDs, three resulted in spontaneous abortion and one resulted in preterm delivery. Two spontaneous abortion cases were exposed to valproate until they miscarried, although a switch to another anticonvulsant was advised at first consultation. Preterm delivery was reported in one case exposed to multiple AEDs (lamotrigine and carbamazepine) and switched to monotherapy in week seven (see details in Table 4). These women had no seizures during pregnancies.

In our study, mothers exposed to antipsychotics and anxiolytics had better pregnancy outcomes. Evidence for the teratogenicitiy of antipsychotic medications is conflicting and hence inconclusive. Use of these drugs in pregnancy may result in toxic effects to the fetus (in the late months) and increase the risk of preterm delivery[28].

An important finding of this study is higher elective abortion rates in cohort cases compared to controls (11.1% vs. 5.1%, RR 2.18, 95% CI 1.09-4.39, p=0.025). There was no evidence of fetal abnormality in these cases, and most elective terminations were performed because of personal reasons. A recent study also reported a tendency to ETOP among women used any type of antidepressants[2]. Antipsychotic medication use during pregnancy was also associated with an increased risk of elective termination[30]. The underlying psychiatric disease, fear of medication effect on pregnancy outcome may play a role in making the decision to terminate the pregnancy. In previous work by Diav-Citrin et al.[31], first-trimester gestational exposure to paroxetine or fluoxetine was evaluated among pregnant women, and the rate of ETOPs was significantly higher in the fluoxetine-exposed group, but not in the paroxetine group. Therefore, it is unclear whether exposure to antidepressants may be correlated with the rated likelihood of pregnancy termination. The authors in this earlier study reported that a higher proportion of the fluoxetine-exposed women who were more likely to terminate their pregnancy had one or more previous ETOPs. In our study, we did not find any difference in previous ETOP proportions between groups. Maternal depression and its association with the perception of teratogenic risk have been previously linked with elective termination of pregnancy[26]. The high and unrealistic perception of teratogenic risk among women and health professionals may lead to terminations of pregnancies. Furthermore, psychiatric disorder itself can often cause this misperception. An accurate information on teratogenic risks and individual risk assessment may help to reduce maternal concerns. It is also important to contact the teratology consulting services for more information relating to chemical exposure and medication in pregnancy[33].

When we evaluated maternal characteristics in this study, we observed that the rate of nulliparity was significantly higher in the drug exposed group (45.2%) than in the control (31.3%). The majority of the pregnant women did not smoke in both groups (see details in Table 1). Smoking rates were higher in women exposed to psychotropic

Table 4: Characteristics of unhealthy outcomes

	Age (years)	Drug(s)	Dose (mg/d)	Exposure in weeks after LMP	Obstetric History	Alcohol/ Smoking	Comments
SA1 (week 8)	29	Escitalopram	10	4-6	Pr. Preg.: 3 Pr. Par.: 1 SA: 2 ETOP: 0	-	Radiation exposure in 4th week, hypothyroidism and L-thyroxine treatment (1000 mcg/d), additional drugs (week 4- 6): cefprozil 1000 mg/d, dexketoprofen 25 mg/d, trimetazidine 40 mg/d
SA2 (week 8)	39	Escitalopram	10	0-5	Pr. Preg.: 1 Pr. Par.: 1 SA: 0 ETOP: 0	-	Hypertension, additional drugs (week 0- 5): zofenopril 30 mg/d, nifedipine 30 mg/d, trimetazidine 40 mg/d
SA3 (week 12)	32	Fluoxetine Mirtazapine Clomipramine	20 30 10	5-12	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	-	Additional drugs (week 5- 12): flurbiprofen 100 mg/d
SA4 (week 12)	22	Sodium valproate	1000	0-12	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	-	Epilepsy for 5 years, continued therapy during pregnancy
SA5 (week 20)	20	Sodium valproate	1500	0-20	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	-	Epilepsy for 7 years, continued therapy during pregnancy
SA6 (week 12)	38	Gabapentin	1200	0-8	Pr. Preg.: 6 Pr. Par.: 5 SA: 1 ETOP: 0	-	Additional drugs (week 0- 8): flurbiprofen 100 mg/d, acemetazin 60 mg/d, diclofenac 50 mg/d, pantoprazole 40 mg/d
BD1	32	Paroxetine	15	0-8	Pr. Preg.: 2 Pr. Par.: 0 SA: 2 ETOP: 0	4 cigarettes/d	Bilateral clubfeet, umbilical hernia, persistent ductus arteriosus, strabismus
BD2	32	Paroxetine	20	7-11	Pr. Preg.: 4 Pr. Par.: 2 SA: 1 ETOP: 1	-	Inguinal hernia, cleft palate, additional drugs (week 7- 11): frovatriptan 2.5 mg/d
PD1	33	Alprazolam	0.5	7-11	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	40 cigarettes/d	Additional drugs (week 7- 8): estradiol 2.5 mg/d, progesterone 12.5 mg/d, amoxicillin 2000 mg/d, naproxen sodium 550 mg/d, loratadine 10 mg/d
PD2	21	Escitalopram	10	2-3	Pr. Preg.: 1 Pr. Par.: 1 SA: 0 ETOP: 0	7 cigarettes/d	Additional drugs (week 2- 3): levofloxacine 500 mg/d, cefprozil 1000 mg/d, etodolac 300 mg/d
PD3	23	Lamotrigine Carbamazepine	100 400	0-7	Pr. Preg.: 0 Pr. Par.: 0 SA: 0 ETOP: 0	-	Continued therapy with lamotrigine 100 mg/d during pregnancy

SA: spontaneous abortion, BD: birth defect, PD: preterm delivery, ETOP: elective termination of pregnancy, d: day, LMP: last menstrual period, Pr. Preg.: previous pregnancies, Pr. Par.: previous parities

medication; it is expected because the psychiatric patients smoke more often than the general population. However, it is remarkable that we encountered no cases of women reported drinking alcohol in pregnancy. Although some reviewers indicated that 15% to 20% of pregnant women reported use of alcohol[34], alcohol consumption varies in different countries and cultures. According to the 2003 World Health Survey, the rate of lifetime abstainers was 92.4% among Turkish women and 99.5% of Turkish women were not using alcohol. On the other hand, several epidemiological studies have indicated a higher frequency of alcohol consumption (10% to 36%) among young female adolescents and university students from the largest cities of the Western

Turkey[35,36]. Although our study was conducted in the second largest city in the Aegean region, no woman reported drinking alcohol while pregnant, may be due to their knowledge or beliefs regarding the potential harm of alcohol use in pregnancy.

Our study has some limitations, including relatively small number of pregnancies and low statistical power. Although the large database studies may seem more reassuring, they also have disadvantages such as lack of detailed clinical information, and a limited ability to control confounds[37]. In this present study, clinical course of psychiatric disorders in the patients was not followed up. Medical treatments were discontinued in most of recognized pregnancies. Only 11% of pregnant women took drugs in all three trimesters. In recent years, there is increasing concern about behavioral teratogenicity of psychotropic medication, particularly for SSRIs. Some investigators reported that maternal antidepressant use was associated with autism spectrum disorder in offspring and recommended long-term follow-up of exposed children[38,39]. However, maternal depression itself can also lead to behavioral and cognitive disabilities in off spring. A genetic predisposition and maternal role modeling may cause children to have psychiatric disorders in adulthood, if mother is mentally ill. Maternal mental illness increases the risk of developing the same disorder in children[40].

CONCLUSIONS

For pregnant women and practitioners, psychotropic medication in pregnancy is still a major dilemma. Treatment with psychotropics or accidental exposure to these drugs in pregnancy should not be considered a reason to terminate pregnancy. Our study shows that there is a tendency to terminate pregnancy among women exposed to psychotropic drugs. We found no increased risk of congenital anomalies, preterm deliveries and miscarriages associated with prenatal psychotropic drug exposure. Nearly half of the drug exposure group attended for prenatal consultation was first time pregnant, so perhaps they had no experience and unrealistic beliefs or concerns about medication use during pregnancy. An accurate risk assessment about drug safety in pregnancy and informing women exposed to drugs may help to alleviate unnecessary fears of the pregnant women and their families.

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