Antidepressant drug exposure during pregnancy. CZTIS small prospective study

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Abstract

OBJECTIVES: Antidepressant drugs are used frequently during pregnancy. The risk assessment of SSRI exposure is still evaluated and re-opened due to studies indicating possible increase of inborn defects, neonatal abstinence syndrome and cognitive ability or behavioral defects.

METHODS: In our study, we prospectively followed groups of pregnancies in years 2002–2009, that were exposed to SSRI. As control group we used 1) women exposed to new atypical antidepressant and anti-psychotics – APD (risperidone, mirtazapine, venlafaxine, trazodone, aripiprazole, ziprasidone, olanzapine), 2) women exposed to nonteratogenic drugs and 3) the general population according to Institute of Health Informations and Statistics (ÚZIS.) Data were analyzed using software Statistica for Windows No.5.5.

RESULTS: The total number of queries on psychotropic drugs performs in CZTIS more than 30% of all calls, constantly. We enrolled a total of 43 women exposed to SSRI and 37 women (1x twins) exposed to new psychotropic drugs (APD) in the study. Exposure to SSRI was often associated with poly-therapy. The most frequent SSRI used were citalopram and/or escitalopram (56%), and setraline (26%). Other SSRI were used sporadically. We observed significantly higher frequency of elective terminations in group of SSRI and higher frequency of abortions a prematurity in APD group. Frequency of malformations does not varied, being in all groups in expected range.

CONCLUSIONS: We confirmed that SSRI exposure during pregnancy was not associated with the higher risk of major malformation. However, number of cases was low and did not allow the statistical treatment with higher power.

Abbreviations:

CZTIS	- Czech Teratology Information Service
ÚZIS	- Institute for Health Informations and Statistics
SSRI	- Selective serotonin re-uptake inhibitors
APD	- Atypical psychotropic drugs
ETOP	- Elective termination of pregnancy
SAB	- Spontaneous abortion
IUGR	- Intrauterine growth retardation
EUROCAT	- European Surveillance of Congenital Anomalies

ORIGINAL ARTICLE

INTRODUCTION

Prevalence of mood and anxiety disorders in women of reproductive age is high, being estimated according to the methodology between 4% and 17.6%. Untreated maternal depression and depressive symptoms have been associated with the risk for negative pregnancy outcomes as fetal growth retardation, preterm birth, lower birth weight, smaller head circumference, and lower Apgar scores (Hemels *et al.* 2005). Selective serotonin reuptake inhibitors (SSRI) are commonly used for treatment, their use has been well documented. They have relatively low rate of side effects. However, studies indicating possible increase of cardiovascular defects, neonatal abstinence syndrome and cognitive ability or behavioral defects have been published as well as others documenting their safety. On the other hand, data for new atypical psychotropic drugs introduced in last years have been insuficient for risk evaluation. More information about effects on embryo development is necessary for both groups.

MATERIAL AND METHODS

The prospective observational study enrolled women, who contacted (on their own initiative or through their health-care providers), the Czech Teratology Information Service (CZTIS) in years 2002–2009. We included calls on exposure during first trimester, time of contact with CZTIS was until 16 week of pregnancy. The data collection at the first contact and follow up were obtained by phone call or by written e-mail questionnaire. A comparison group comprised queries regarding 1) exposure to other psychotropic drugs, 2) exposure to non-teratogenic and non-psychotropic exposures, and 3) general population according to data published by Institute of Health Information and Statistics of the Czech Republic. The demographic parameters, medical and obstetric history and details of exposure were obtained after enrollment in the study. After delivery, the pregnancy outcome was ascertained. Risk of malformations in general population was estimated according to data published by ÚZIS for relevant years, which is in agreement EUROCAT (European Surveillance of Congenital Anomalies) estimating frequency of malformation in population on 2–3%.

Statistical analysis

Student *t*-test was used for the statistical comparison of demographics, X square and Fischer test were used for comparison of the pregnancy outcomes, $p<0.05$ was considered statistically significant. All data were analyzed with the statistical software Statistica for Windows 5.5 (StatSoft, Tulsa, OK).

RESULTS

A total of 43 women exposed to SSRI and 37 women (1× twins) exposed to new psychotropic drugs (APD) were enrolled in the study. Majority of women treated by SSRI were exposed to citalopram (36.84%), escitalopram (26.31%), or sertralin (28.94%). The exposure to the other drugs was lower: paroxetin 7.89%, fluoxetin 10%, and fluvoxamin 2.63%. The control group exposed to APD was heterogenous including antidepressant as well as antipsychopic (risperidone 15.4%, mirtazapine 20.5%, venlafaxine 28.2%, trazodone 15.4%, aripiprazole 5.1%, ziprasidone 2.6 %, olanzapine 7.6 %, quetiapin 5.1%) introduced on market in last years without knownledge of the risk during pregnancy. Ten cases were included in both groups exposed to both, SSRI and APD. Depression was the main indication for treatment in both groups, however schizophrenia or anxiety were included in both groups, too. We enrolled 85 women in control group 2 from the same period, which compriced women exposed mainly to hormonal contraception, common antibiotics (as penicilins, cephalosporins, macrolides) used for disease without hyperthermia, vaccination by inactivated bacteria or viruses considered safe during pregnancy, paracetamol, or antihistaminics. There were no significant differences in age, number of previous pregnancies and other demographical parametres in all three groups. Smoking rate and alcohol consumption were slighly higher in the depressed women in comparisson with group 2. Majority of pregnancies in SSRI and APD groups were exposed more than one psychotropic drug during all pregnancy. The exposure to SSRI was associated with poly-therapy in 86% versus 54% in APD.

Pregnancies exposed to SSRI resulted in birth of 37 children, 9 elective abortions (ETOP) and 5 spontaneous abortion and 1stillbirth. Two birth defects were identified in this group – sub-aortic defect of ventricular septum (minor malformation) after exposure to fluoxetine and bilateral clubfoot (major malformation) after exposure to sertraline. Both cases were exposed to polytherapy.

Pregnancies exposed to APD resulted in 28 live birth children, 1 elective abortion (ETOP) and 10 spontaneous abortions. Also in this group were identified two inborn defects, microcephaly (major malformation) and hemangioma (minor malformation), both after venlafaxine exposure.

Control group comprising nonteratogenic exposure resulted in live birth of 78 offspring, 2 elective terminations and 5 spontaneous abortions. In this group only 1 inborn defect was identified – coarctation of aorta. Documented malformation expressed no specific pattern and only one minor malformation of cardiovascular system was identified in SSRI exposed offspring. Incidence of malformations for general population according to EUROCAT and ÚZIS is 2–3%.

Tab. 1. Pregnancy outcome. Pregnancies exposed to SSRI were shorter, however weight and lengh were not different from control. APD exposed pregnancies were shorter with lower weight and lengh.

	Duration pregnancy	Exposed / Control $p<0.05$	Weight (g)	Exposed / Control $p<0.05$	Length (cm)	Exposed / Control $p<0.05$
SSRI	39.214	$p=0.014089$	3450	$p=0.256345$	51.65	$p=0.296278$
APD	38.3	$p=0.025541$	2911	$p=0.000022$	47.87	$p=0.000214$
Control	39.89		3762		50.27	

Pregnancies were significantly shorter in both psychotropic drug exposed groups in comparisson with control 2. Significantly lower birth weight and length was revealed in APD exposed pregnancies in comparisson with both SSRI exposed and control group 2. Both lengh and weight were also lower in SSRI exposed group, however differences were not statistically significant (Table 1).

Both ETOP and spontaneous abortion were found in lower incidence in control group 2 than in unexposed population (ÚZIS). In SSRI group, there was higher incidence of ETOP, but it was not higher compared with general population according to ÚZIS (18.5%).

On the other hand, there was higher frequency of spontaneous abortions in APD group compared with control 2 and SSRI group. It was almost two folds higher than for general population (10%) (Figure 1). If we compared group of women experienced spontaneous abortion with others exposed to antidepressant, they had contacted CZTIS significantly earlier than those gave birth to the live children (week 5.1 versus 10.3 in SSRI group; week 6 versus 8 in APD group). On the other hand, we were not able to demonstrate dependence on dose or polytherapy. The ÚZIS data include also very early period similary to SAB group, whereas contact at the end of first trimestr decreases the risk for spontaneous abortion, because such cases are not included in our database, if women contact CZTIS later during pregnancy.

DISCUSSION

In recent years, SSRI have been increasingly used for the depression treatment during pregnancy (Cooper *et al.* 2007). As untreated depression may have severe consequence for the child as well as for the mother, the mental disorder have to be treated. Reports of inborn defects (Bar-Oz *et al.* 2007; Scialli 2010), neonatal withdrawal symptoms (Klinger & Merlob 2008) and persistent pulmonary hypertension (Andrade *et al.* 2009) increased concern regarding the use of SSRIs during pregnancy. The potential risk of exposure have to be weighed against the risk of depression relapse, if the medication is discontinuated. Lower birth weigh and shorter birth length were reported as result of severe anxiety during second and third trimester (Hosseni *et al.* 2009) as well as the consequence of severe depression and other mental illnesses (Jablensky *et al.* 2005). Population based case control studies found slighly higher risk of major malformation in women, who suffered panic disorder during pregnancy (Acs *et al.* 2006).

The number of pregnancies, that have been exposed to psychotropic drugs, has performed in our center constantly more than 30% of all calls. Depression was the most frequent diagnosis in such cases. All pregnancies included in study were exposed to the drugs during the first trimester and majority of them (75% pregnancies exposed to SSRI and 81% exposed to ADP) until the birth. SSRI were frequently used during pregnancy for treatment of depression and anxiety, new psychotropic drugs were used for their treatment in pregnancy, too. However, follow up in pregnancies exposed to the psychotropic drug was lower then in other chronic diseases.

Several studies have observed an increased risk for preterm birth and low birth weight in SSRI-exposed pregnancies (Toh *et al.* 2009; Ellfolk & Malm 2010). We found higher frequency of ETOP in group of SSRI-exposed pregnancies, however there was not higher frequency of SAB and premature birth compared with

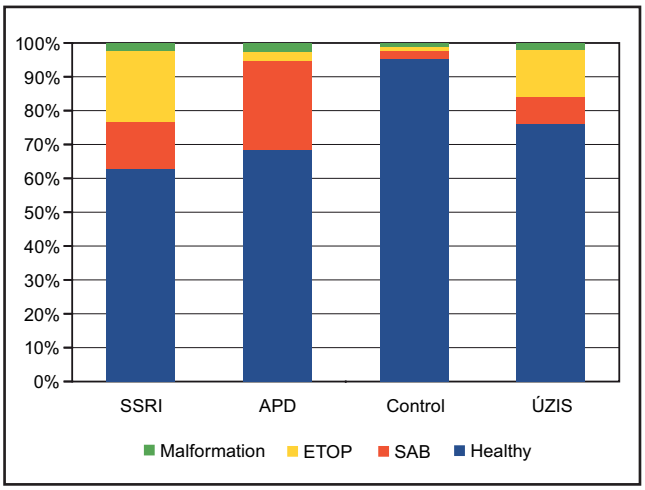

Fig. 1. Pregnancy outcomes. SSRI- exposed pregnancies were associated with higher frequency of of ETOP, ADP- exposed pregnancies (control 1) were associated with higher frequency of SAB. Control group (2) has lower occurence of ETOP and SAB than published by ÚZIS for population (control 3). Risk of malformation was not different in all groups.

controls exposed to non-teratogenic drugs. Higher frequency of SAB and preterm deliveries were published also for other antidepressants (Nakhai-Pour *et al.* 2010). In ADP group was significantly higher number of spontaneous abortion and premature birth, that is in agreement with published studies . In our group of SSRI-exposed pregnancies prevailed citalopram/escitalopram use. Citalopram is considered one of the most safe from this group. Spontaneous abortions occured in both groups exposed to antidepressant in the women, who have contacted CZTIS significantly earlier than those, who gave birth to live children. It may explain higher frequency of SAB in APD group, because the women suffering severe disease tend to contact CZTIS earlier during pregnancy or even before it. We suppose that preterm delivery associated with lower birth weight may result from poly-therapy or worse disease course. Drug doses within therapeutic range were without association with negative pregnancy outcome. Even very high dose in woman, who attended suicide, or the combination with anticonvulsant (lamotrigine or clonazepam) resulted in the birth of normal child. On the other hand, low dose of citalopram was associated with SAB. Frequency of SAB or elective abortion after the exposure to different drugs was not determinant, as number of pregnancies was too low to allow to exclude the accidental accumulation of the negative pregnancy outcomes. It may be demonstrated on citalopram/escitalopram exposure that resulted in 21.5% SAB for citalopram in comparison with 10% for escitalopram. Moreover, the pregnancies resulting in SAB were exposed also to APD, moreover one woman suffered hyperemesis and diabetes type I, which increase risk for negative pregnancy outcome.

This small study is in agreement with previous ones. The structural malformations according to our study do not represent higher risk than expected in unexposed population. Our study contributes the data to the knowledge regarding antidepressant exposure during pregnancy.

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