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Letter to Editor

Use of specific SSRIs and birth defects

Prof. dr hab. n. med. Dominika Dudek
Editor-in-Charge of "PsychiatriaPolska"

Dear Professor,

On 08.07.2015 in the "British Medical Journal" an article entitled: Specific SSRI and birth defects :bayesian analysis to interpret new data in the context of previous reports, by J. Reefhuis, (National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA), O. Devine (National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA), JM Friedman (Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada), C. Louik (Slone Epidemiology Center at Boston University, Boston, MA, USA) and MA. Honein (National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA) was published. The article showed new, important data concerning pharmacotherapy of depression during pregnancy.

The aim of the study was the assessment of associations between use of selective serotonin reuptake inhibitors (SSRIs, fluoxetine, sertraline, paroxetine, citalopram, escitalopram) during first trimester of pregnancy and specific birth defects [1].

Reports (collected in US National Birth Defects Prevention Study (NBDPS)) of children born with birth defects in the US states of: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah were analysed. Cases of live born, stillborn or induced abortions (between 2002 and 2009) with one of 30 major birth defects were included. Cases with known chromosomal or monogenic disorder were excluded. Information regarding SSRI use was obtained from mothers in a telephone interview between six weeks and two years after the estimated time of

delivery. It should be emphasised, that no specific question regarding depression was present in the questionnaire. Women were asked about presence of any illnesses and its treatment. Moreover, they could report use of: Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), Celexa (citalopram) in the period from three months prior to the conception to the childbirth. There was no question for Lexapro (escitalopram).

Women reporting taking one of the SSRIs at least once in the period from one month before conception through the third month of pregnancy were considered for analysis. Women exposed to more than one type of SSRI were included in the "multiple SSRI" category. Mothers were classified as "unexposed" if they did not take any antidepressants during the period from three months before to the end of the pregnancy and were not diagnosed with depression, anxiety, bipolar disorder or obsessive-compulsive disorder. Women, who used antidepressants other than the SSRIs (for example venlafaxine), used antidepressants in a different period or who did not answered drug-related questions were excluded from the analysis.

On the basis of NBDPS data, 17,293 unexposed cases, 659 birth defects cases exposed to one of the SSRI (citalopram, escitalopram, fluoxetine, paroxetine, sertraline), 9,559 unexposed controls and 298 controls exposed to one of SSRI were included into analysis.

It was shown, that fluoxetine treatment in the early pregnancy was associated with ventricular septal defects, right ventricular outflow tract obstruction and craniosynostosis in infants.

Significant associations were also observed between paroxetine treatment and anencephaly, atrial septal defects, right ventricular outflow tract obstruction, gastroschisis and omphalocele.

It should be emphasised, that cardiac birth defect – right ventricular outflow tract obstruction in infants of mothers who used fluoxetine or paroxetine in early pregnancy was reported previously in the literature [2]. Similarly, cases of anencephaly [3] and atrial septal defects [4] after use of paroxetine were described.

Odds ratios (ORs) for maternal paroxetine treatment and anencephaly was 3.2 and for right ventricular outflow tract obstruction was 2.4, respectively. It was evaluated, that the absolute risks for anencephaly and right ventricular outflow tract obstruction in the children of women who were treated with paroxetine early in pregnancy would increase from 2 to 7 per 10 000 and from 10 to 24 per 10 000, respectively.

It should be stressed, that this study did not confirm previous reports on relation between sertraline use and birth defects [5, 6], despite the fact that 40% of women included in the analysis reported use of sertraline during early pregnancy. Moreover, 14 other previously reported relations between SSRIs exposition and birth defects were not supported in the analysis.

However, the article confirmed, that SSRIs should not be considered as pharmacologically homogenous group. It was known before, that SSRIs differ in pharmacokinetics, now the study showed, that they also may differ in its teratogenic potential.

The limitations of the study is fact that it did not include other diseases of the mothers and other factors, which could potentially play the role in the development of birth defects. Moreover, data were obtained from women during a telephone interview

between six weeks and two years after the estimated date of delivery and were not confirmed by healthcare staff. Neither a dose nor a duration of treatment were noted. No information about substance abuse (alcohol, psychostimulants, tobacco) were included. It should be stressed, that also single exposure was considered as a "drug use".

The second important article, which also was published in the "British Medical Journal" (on 17.04.2015) is Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design, by Kari Furu, Helle Kieler, Bengt Haglund, Anders Engeland, Randi Selmer, Olof Stephansson, Unnur Anna Valdimarsdottir, Helga Zoega, Miia Artama, Mika Gissler, Heli Malm, Mette Nřrgaard [7].

Data for the second study were obtained from national health registers of Denmark, Finland, Iceland, Norway and Sweden and included all the cases of children born between 1996 and 2010, with major birth defects diagnosed within 365 days after birth. The use of drugs was confirmed by checking, if the mother of the child filled the prescription for an SSRI from 30 days before the first day of the last menstrual period until the end of the first trimester (97 days after the last menstrual period).

In total, 36,772 (1.6%) cases of infants exposed to a SSRI or venlafaxine during the first trimester were included in the analysis.

Major birth defects were diagnosed in 1,357 children (3.7%), compared to 71,374 (3.2%) of unexposed infants (the group consisted of 2,266,875 children). Frequency of overall cardiac birth defects among infants exposed to SSRIs or venlafaxine was 1.5% and in control group – 1.2%. In-utero exposure to venlafaxine, fluoxetine, paroxetine, sertraline or citalopram was associated with atrial or ventricular septal defects. The prevalence of right ventricular outflow tract obstructions or clubfoot was increased after exposure to any SSRI. After exposure to paroxetine or fluoxetine prevalence of cardiovascular defects increased by 30%. Moreover, after exposure to fluoxetine and paroxetine prevalence of septal defects increased by 45% and 40%, respectively.

The results from above studies suggest, that use of fluoxetine and paroxetine in early pregnancy may be associated with more frequent occurrence of some cardiovascular birth defects.

Yours sincerely
Ewa Bałkowiec-Iskra
Warsaw, 26.08.2015

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