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COMMENTARY

The Nordic health registers – an important source when evaluating the safety of antidepressants during pregnancy

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Abstract: Depression during pregnancy occurs frequently and selective serotonin reuptake inhibitors (SSRIs) are often the drug of choice when treating pregnant women. Most published studies found no increased risks of congenital malformations in association with SSRIs, but there are reports of various malformations for SSRIs as a group and for specific SSRIs. To assess potential adverse effects of SSRIs as one group may be questioned because of their dissimilarities and very large datasets are needed when studying specific SSRIs. The national health and population registers in the Nordic countries offer excellent opportunities to assess long term effects of exposure during fetal life. As each of the Nordic countries is small, collaborative studies including information from all the Nordic countries are warranted to fully understand risks associated with exposure to antidepressants in fetal life.

Keywords: antidepressive agents, adverse effect, pregnancy, multicenter study

Selective serotonin reuptake inhibitors (SSRIs) have been used extensively for the treatment of depression, including pregnant women during the last few decades. Though the data so far available show that SSRIs are not major teratogens, there are reports of various malformations for SSRIs as a group and for specific SSRIs.[1–9] Moreover, as depression in itself might affect the fetus adversely the question whether it is safer to stop rather than continue medical treatment for depression when a woman becomes pregnant remains unsolved. Several of the antidepressants might also be used with indicators other than depression such as anxiety and pain conditions. In Europe and the US, the regulatory authorities recommend that SSRIs should only be used when the benefits outweigh the risks, but such recommendations are difficult to follow when the risks are not fully known. Consequently, well-performed studies such as the study by Kornum et al assessing the safety of antidepressants during pregnancy are warranted.[10] The authors present an updated analysis of SSRI use and risk of congenital malformations using data from regional and national registers in Denmark.

Depression during pregnancy occurs frequently and estimated rates vary from 7% to 25%.[11] Relapses during pregnancy have been reported to be about 50% and the discontinuation of medication because of anticipated risks might explain some of this high rate of relapse.[12] Most of the women included in the study by Kornum et al were included between 1997 and 2006 and during this period use of SSRIs during pregnancy in Denmark increased from 0.3% to 2.4%. The trend of an increased use of SSRIs during pregnancy has been reported from other countries and the recurring reports of risks with SSRIs during pregnancy seem to have had no effect on this

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trend.[13] One should also recall that although use of SSRIs is increasing in the general population and among pregnant women, major depression seems to be undertreated in general with only a minority with signs of major depression receiving treatment.[14]

Serotonin, which is mainly found in the central nervous system, the intestinal wall, and in large constricted blood vessels has a variety of functions such as effects on mood and behavior as well as vasoconstrictive properties. Depressed individuals have decreased concentration of serotonin metabolites in the cerebrospinal fluid and brain tissues. SSRIs are antidepressants that inhibit the reuptake of serotonin into the pre-synaptic cell and initially increase the level of serotonin available to bind to the post-synaptic receptor. In accordance with previous studies, Kornum and coworkers analyzed risks of SSRIs as one group (ATC-code N06AB), but also risks associated with specific SSRIs such as escitalopram, citalopram, sertraline, fluvoxamine, fluoxetine, and paroxetine.[1–10,12] The different SSRIs have varying degree of selectivity for serotonin and the other monoamine transporters and may vary in potency, pharmacokinetics, and metabolism. The acute increase in serotonin levels is probably not the whole explanation of the mechanism of action of SSRIs, which largely remains unknown and so does the mode in which SSRIs may exert their potential teratogenic effect. In this context it is important to note that other antidepressants such as clomipramine with ATC-code N06AA and venlafaxine (N06AX) also affect the reuptake of serotonin and have selectivity for serotonin. In the study by Kornum et al these two drugs were grouped with other non-SSRI antidepressants and for which they found no increased risks of congenital malformations.[10] As the authors point out specific SSRIs could have different teratologic effects and consequently they should ideally not be evaluated as one entity. However, for practical reasons, and mainly due to limited statistical power in most of the previous studies SSRIs have been studied as one group. In some studies risks have been assessed for the specific SSRIs most frequently used and the reported findings with increased risks for cardiac malformations with paroxetine might partly reflect its dominant role on the market in the earlier years.[1,2,5,6] Though citalopram was the most prevalent drug in the present study, use of escitalopram has increased several-fold in the Nordic countries during recent years. Kornum et al found a doubled risk for malformations in general and even higher risks for cardiac malformations and septal heart defects among users of escitalopram. As escitalopram is the active enantiomer of citalopram and the drugs are similar concerning reuptake inhibition of serotonin and selectivity for serotonin, the finding of no or only slightly increased risks for citalopram is surprising considering the increased risks with escitalopram. Future studies may reevaluate whether antidepressants should be grouped according to SSRIs or non-SSRIs, serotonin selectivity, or other criteria when assessing potential adverse effects, at least when limited power does not allow analyses of specific antidepressants.

As illustrated in the study by Kornum et al the national health and population registers in the Nordic countries offer excellent opportunities to assess long term effects to exposure during fetal life.[10] Through the 10 or 11 digit code assigned to each citizen in the Nordic countries, included in the national and in some regional registers, it is possible to link information from different registers and thereby follow each individual from the beginning of life until death. The national registers in the Nordic countries, which are constructed in a similar way and with similar contents have been used for numerous studies and contributed to shed light on important scientific questions. However, with opportunities come responsibilities. Access to these rich data sources does not necessarily mean that the information can be used unrestricted. Rare exposures and rare outcomes demand very large databases and as each of the Nordic countries are small countries with a population ranging from 300,000 in Iceland to 9 million in Sweden, the data in each country are probably too sparse to evaluate associations between specific drugs and specific malformations or other rare outcomes. The limited size of the study by Kornum and coworkers is only partly compensated by their comprehensive analyses. Some questions such as the implication of the underlying psychiatric disease were left unanswered and others would have needed a much larger dataset. A large dataset could have been accomplished by combining information from the health registers in the Nordic countries. Women planning a pregnancy and their physicians are entitled to get as reliable information as possible concerning risks with medication that can be used during pregnancy and this can only be achieved through rich data sets combined with high quality studies.

Disclosure

The author reports no conflicts of interest in this work.

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