

THE EFFECT OF ASCERTAINMENT BIAS IN EVALUATING GESTATIONAL ANTIDEPRESSANT EXPOSURE

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ABSTRACT

Several administrative database studies have reported on a positive association between first trimester exposure to paroxetine and ventricular septal defects (VSD). Using multiple source data, we have shown that depressed women utilize significantly more health care resources, including ultrasound, echocardiogram and emergency room visits for their babies. Hence, there is much higher chance to identify VSD in their babies than among healthy controls. Moreover, paroxetine has been used more specifically than other SSRI for anxiety, further increasing the chance of ascertainment bias.

Large numbers of women of reproductive age suffering from depression and anxiety are prescribed selective serotonin reuptake inhibitors (SSRI) or selective norepinephrine-serotonin reuptake inhibitors (SNRI). While originally these classes of drugs were reported not to increase the rates of major malformations¹ some recent studies and meta-analyses suggest an increased risk for cardiac malformations.^{2,3} These reports, if correct, should lead to change in the way we counsel expecting women treating their depression or anxiety with these classes of drugs.

In a large prospective cohort study, recently conducted by us, on the rates of cardiac malformations in infants exposed during the first trimester to paroxetine, we found identical rates of cardiac malformations (0.7%) in exposed and control cases, a rate identical to reference values by pediatric cardiology texts.⁴ This has led us to undertake a deeper look into potential sources of bias, which may lead to a detection of a false signal, claiming these drugs teratogenic when in fact they may not be.

If women taking SSRIs or SNRIs are more likely than other women to undergo diagnostic tests that detect cardiac malformations, then the apparent higher rates of such malformations may constitute an ascertainment bias. Why would women on antidepressants have such tests more often? There are two obvious reasons:

1) Their condition is often associated with anxiety and fears of having a malformed child.

Studies have shown that women with depression and/or anxiety utilize significantly more health care services for their infant children than healthy women.⁵⁻⁶

To quantify the use of ultrasound, echocardiogram, and amniocentesis during pregnancy, we employed several administrative databases from the Province of Quebec: La Régie de l'Assurance Maladie du Québec (RAMQ), Med-Écho, and Le fichier des événements démographiques du Québec (birth and death registries) of l'Institut de la Statistique du Québec (ISQ).⁷⁻¹⁰

We found that women using antidepressants during pregnancy had significantly higher mean number of ultrasounds, amniocentesis and echocardiograms than women not receiving antidepressants.¹¹ Women who received any SSRI had more than two-fold likelihood to have undergone echocardiogram in the first year of life compared with infants of women not receiving antidepressants.¹¹

Putting these data into clinical context: if a woman on an antidepressant has twice as many echocardiograms than the next woman, she has a substantially higher chance of detecting a child with a cardiac malformation who was clinically undetected. This means that studies suggesting two-fold increased odds ratio (OR) of cardiac malformations associated with SSRI are actually having OR of:

$$\frac{2}{2} = 1$$

2) With the wide publicity of presumable cardiac defects caused by SSRI and SNRI, it is likely that women who hear this news will be tested more commonly than “control” unexposed women.¹²

To make things even more putative, the most common cardiac malformation is ventricular septal defect, (VSD), and the majority of VSD are of the muscular type, which tends to close during toddlerhood.¹³ This means that in the control group many cases will “disappear” and will not be detected by later echocardiogram, further increasing the risk of ascertainment bias. Unless this source of serious bias is acknowledged and accounted for, women who need antidepressants will continue to be scared off these medications with serious risks for their health and well being.¹⁴

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CPNDS Symposium available online:
Vol 18(1):e76-e175

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