Observational/Non-Interventional Registration Information

Unique Protocol ID: 13947

Brief Title: Meta-analysis of observational studies on first-trimester fluoxetine exposure and major fetal malformations

Official Title: Meta-Analysis of Published Observational Studies on the Association between Fluoxetine Exposure during the First Trimester of Pregnancy and the Risk of Major Fetal Malformations

Secondary IDs: B1Y-MC-B003

Study Type: Meta-Analysis

Sponsor: Eli Lilly and Company

Collaborator(s): None

Brief Summary: A meta-analysis of epidemiological studies published in peer-reviewed journals up to April 7, 2009 was conducted to assess the potential association between first trimester fluoxetine exposure and the risk of major fetal malformations, with a particular focus on major cardiovascular defects. Inclusion criteria were established a priori. Eight (8) articles were eligible for inclusion in the analysis.

Overall Status: Completed

Study Start Date: March 2009

Study Completion Date: July 2009

Study Design:
Study Model: Meta-analysis

Enrollment: N/A

Outcome Measures: Major fetal malformations, with a particular focus on major cardiovascular defects

Conditions or Focus of Study: Infants of depressed women exposed to fluoxetine during the first trimester of pregnancy compared with infants of women not exposed to fluoxetine during the first trimester of pregnancy.

Sample Population Description: Varied by study and ranged from national birth defects registries to observational studies with limited sample size

Literature Search Method:

A search of the literature in PubMed and EMBASE up to April 7, 2009 was performed to identify cohort and case-control studies assessing the risk of major fetal malformations and fluoxetine exposure during the first trimester of pregnancy. The following search terms were used: *fluoxetine, Prozac, SSRIs OR selective serotonin reuptake inhibitors, antidepressant, antidepressive agents,* combined with *birth defects, congenital anomalies, congenital malformations, congenital abnormality, fetal anomaly, fetal malformation, fetal abnormalities, cardiac defects, heart defects, pregnancy outcomes, birth outcome, neonatal outcome, obstetric outcome*.

Eligibility Criteria:

Priori-specified Inclusion Criteria:
Publication in English, study in human use, a nonfluoxetine exposure comparison group, cohort, or case-control study, providing information regarding fluoxetine use during the first trimester of pregnancy and major fetal malformation/major cardiovascular defects.

Priori-specified Exclusion Criteria:
Animal experimental studies, editorials, abstracts, case reports, case series studies, epidemiological studies without comparison group(s), studies not published in English, and studies reported in non-peer reviewed media such as internet were excluded.

Gender: Females

Age Range: Child-bearing ages

Results:

Eight (8) studies (4 prospective cohort studies, 2 retrospective cohort studies, and 2 case-control studies) met the criteria for inclusion in the meta-analysis. The studies included in the meta-analysis were Pastuszak and colleagues (1993), Chambers and colleagues (1996), Malm and colleagues (2005), Alwan and colleagues (2007), Louik and colleagues (2007), Diav-Citrin and colleagues (2008), Oberlander and colleagues (2008), and Einarson and colleagues (2009). Of note, the Swedish Registry study (Källén and Otterblad 2007) was excluded from the primary analysis of meta-analysis because the outcome in the Swedish Registry study was “malformation” which included “minor conditions of little clinical significance” while the outcome of the meta-analysis was major malformations; nevertheless, the Swedish Registry study was included in post-hoc analyses.

The results of this meta-analysis indicated an odds ratio of 1.34 (95% confidence interval [CI]: 0.98 to 1.83; p=0.062) for major fetal malformation in depressed women exposed to fluoxetine during the first trimester of pregnancy compared to women not exposed to fluoxetine. The meta-analysis also showed an odds ratio of 2.92 (95% CI: 1.29 to 6.58; p=0.025) for major cardiovascular defects in depressed women treated with fluoxetine during the first trimester of pregnancy compared to women not exposed to fluoxetine. However, post hoc analyses for major cardiovascular defects showed variable results from primary analysis - cohort studies and case-control studies combined: OR=1.23, 95% CI: 0.60 to 2.53, p=0.573; cohort studies plus the large Swedish Registry Study with a sample size of 873,876: OR=1.43, 95% CI: 0.83 to 2.47, p=0.143.

Limitations:

- The control groups consisted mainly of non-depressed women and the meta-analysis did not control for depression status, therefore the results from this meta-analysis was confounded by possible effects due to depression per se or highly comorbid behavioral risks, such as smoking and substance/alcohol use or abuse.
- Confounding information was not systematically collected in the included studies; thus, this meta-analysis did not control for any confounding factors such as age, alcohol drinking, other underlying diseases, and family history of congenital malformations.
- This meta-analysis only focused on published studies in English. It is possible that some valid epidemiological data, either unpublished or published in a language other than English, were missed in this analysis.

Addendum:

Additional publications on fluoxetine and major fetal malformations have been identified since the completion of meta-analysis. An updated meta-analysis is ongoing to incorporate the newly eligible studies and the updated Swedish registry study.

References:

Alwan S, et al. *N Engl J Med* 2007; **356**: 2684–2692.
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Diav-Citrin O, et al. *Br J Clin Pharmacol*; 2008; **66**:695–705.
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Louik C, et al. *N Engl J Med* 2007; **356**: 2675–2683.
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Pastuszak A, et al. *JAMA* 1993; **269**: 2246–2248.