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Are antidepressants safe in pregnancy? A focus on SSRIs

Catherine took paroxetine 20 mg daily 3 years ago at the age of 32 for symptoms of depression from a difficult divorce. She only took it for 2 weeks as it made her feel nervous. Her depression lifted after 6 weeks. She has remarried and she and her new husband were discussing whether to have children, when she discovered that she was 2 months pregnant. She is now experiencing the same symptoms she had 3 years ago and asks her family physician whether she should take an antidepressant. What does the evidence show?

In British Columbia selective serotonin reuptake inhibitor (SSRI) antidepressant use in pregnancy more than doubled, from 2% in 1998 to 5% in 2001.[1] Use in Quebec also doubled over the same period,[2] and in 7 U.S. health plans (n=118,935) use grew from 2% in 1996 to 8% in 2004-5.[3]

Are pregnant women at higher risk for depression?

Pregnancy does not lead to higher rates of depression.[4] A systematic review estimates a point prevalence of 3.1%-4.9% per trimester, with 7.5% of women experiencing a new episode of depression during pregnancy.[4] A nationally representative U.S. survey found similar rates of depression in pregnant and non-pregnant women: 5.6% vs. 8.1%.[5]

Does depression in pregnancy lead to harm?

Depression in pregnancy is associated with an increase in prematurity, low birth weight, poor Apgar scores, need for neonatal intensive care, gestational hypertension and pre-eclampsia, operative deliveries, postpartum depression, poor nutrition, smoking, alcohol and drug use.[6] However, these studies fail to establish whether depression leads to harm, or whether poorer outcomes are due to an association of depression with factors such as poverty, poor living conditions, lack of social support, and difficult previous pregnancies.

What are the benefits to the mother of SSRIs in pregnancy?

There is no randomized controlled trial (RCT) evidence of benefit; no RCTs have compared SSRIs in pregnancy with non-drug treatments, no treatment or other antidepressants. One frequently cited cohort study (n=201) compared discontinuation of antidepressants for ≥1 week with ongoing use in pregnancy.[7] Mean prior depression duration was >15 years; 43% of participants relapsed in pregnancy, including 31% of ongoing users and 68% of those discontinuing use. The authors do not report on withdrawal reactions, no protocol is described for gradual dose reduction, and timing of many relapses suggests withdrawal effects rather than a relapse. Quality of life, functioning, serious and total adverse events, and birth outcomes were not reported.

Publication bias has led to estimates of SSRI efficacy that are exaggerated by one-third in depressed non-pregnant adults.[8] SSRIs failed to differ from placebo to a clinically distinguishable extent for mild or moderate depression.[9] A meta-analysis comparing drug and non-drug treatments for depression found no difference in general; SSRIs were more effective than psychotherapy to a small, clinically meaningless extent, and psychotherapy was as effective for severe as for milder forms of depression.[10]

What are the benefits to the infant of SSRIs in pregnancy?

Eight cohort studies with concurrent controls have compared antidepressants to no treatment in women with depression. Three were population-based administrative database analyses, two in British Columbia[1,11], and one in a U.S. health plan, Group Health.[12] The other five studies were mainly clinic-based (n=44-107).[13,14,15,16,17] These studies provide no evidence that SSRI use improves infant health. Mortality was not examined. Neonatal intensive care use did not differ significantly (n=268; 4 studies): 16.6% on SSRIs vs. 8.6% no drug. Birth weight also did not significantly differ (n=2,279; 6 studies): mean 3.36 kg on SSRIs vs. 3.53 kg no drug. There were more pre-term births on SSRIs (n=548; 3 studies): 11.8% vs. 4.7%, RR=2.2 (95% CI 1.2-4.1),

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NNH=14; and more infants had respiratory distress at birth (n=1,743; 2 studies): 12.4% vs. 8.2%, RR=1.6 (95% CI 1.2-2.1), NNH=24.

What are the harms to the fetus of SSRIs in pregnancy?

Miscarriages: SSRI use was associated with more spontaneous abortions in a cohort analysis of women contacting a teratology information service (n=1,874)[18] and a meta-analysis of 6 cohort studies.[19]

Cardiac defects: Paroxetine is the only SSRI subject to regulatory warnings of teratogenic risks. A GSK meta-analysis of 14 observational studies to 2008 (10 controlled cohort analyses and 4 case-control studies) found an increase in cardiac malformations, RR=1.5 (95% CI 1.2-1.8), NNH ~200, and total malformations, RR=1.2 (95% CI 1.1-1.4).[20] Effects were broadly consistent across settings and research methods.

A class effect appears likely. In an 8-year follow-up of all births in Denmark, 0.9% of women who had filled at least 2 prescriptions for SSRIs during pregnancy (n=1,370) had infants with septal heart defect, versus 0.5% of unexposed women (n=493,113), OR=2.0 (95% CI 1.1-3.5), NNH=246.[21] Women exposed to more than one SSRI were at higher risk, OR=4.7 (95% CI 1.7-12.7), NNH=62, versus no exposure. Citalopram, sertraline and any SSRI use were implicated.

In a tertiary care centre in Israel in which all infant heart murmurs were investigated with echocardiography, congenital heart defects were found in 3.4% of babies with 1st trimester SSRI exposure and 1.6% of non-exposed, RR=2.2 (95% CI 1.1-4.4).[22] A Dutch study found that children with continuous prenatal SSRI exposure (n=197) had more cardiac surgeries than unexposed children (n=36,998) OR=5.6 (95% CI 1.9-16.3) despite similar rates of diagnostic tests.[23] Two studies examined infant cardiac malformation rates among women on SSRIs as compared to non-users with a depression diagnosis and failed to find a difference (n=10,878) RR=1.3 (95% CI 0.7-2.1).[11,12]

Persistent pulmonary hypertension of the newborn (PPHN): PPHN occurs in around 1 per 1000 live births and is potentially fatal.[24] A case-control study found an over 5-fold increased rate of PPHN in infants exposed to SSRIs after the 20th week of pregnancy.[25] A Swedish national birth registry analysis of women exposed to SSRIs late in pregnancy (n=2,350/831,324) also found increased risks of PPHN: RR=3.6 (95% CI 1.2-8.3).[26] Two U.S. studies failed to confirm this effect, but both were underpowered to find a difference.[27,28]

Poor neonatal adaptation: irritability, persistent crying, tremor, restlessness, feeding difficulties and sleep disturbance have been reported in 20-30% of infants following 3rd trimester exposure.[29,30] Symptoms are mainly mild and transient, but convulsions can occur and some infants require intubation. Serum concentrations of paroxetine were higher in infants with poor neonatal adaptation compared with those without symptoms, despite similar maternal paroxetine dose.[31] Longer-term adverse developmental and cognitive effects remain largely unknown.

Non-drug treatments

Non-drug treatments are generally poorly tested in pregnancy. One 16-week RCT (n=38) evaluating interpersonal psychotherapy[32] and an 8-week RCT (n=150) of acupuncture[33] found a reduction in depression symptoms.

Conclusions and clinical implications:

- There is no evidence that SSRIs in pregnancy improve maternal or infant health, and substantive evidence that they pose a risk to the fetus. **Thus the harms exceed the benefits in this setting.**
- Non-drug options such as cognitive behavioural therapy or psychotherapy are also unproven, but do not carry a risk to the fetus. The common argument of their lack of availability is not relevant for this relatively small, high priority population.
- If a woman wants to stop SSRIs in pregnancy, it is best to taper the dose over at least 1 week to minimize withdrawal symptoms.
- Exercise, social support, sleep hygiene and good nutrition are important for all pregnant women, including those with symptoms of depression.

NNH = number needed to treat to cause one harmful event
RR = relative risk CI = confidence interval OR = odds ratio

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For the complete list of references, including citations 10-33, go to: http://ti.ubc.ca/letter76#1

The draft of this Therapeutics Letter was submitted for review to 55 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.