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Safety of SSRIs in Pregnancy

Depression occurs in up to 20% of pregnant women, and the use of selective serotonin reuptake inhibitors (SSRIs) in these women has been increasing.[1] Maternal depression has itself been associated with intrauterine growth problems and low birth weight, so the risks of exposure to antidepressants during pregnancy must be weighed against the risks of untreated depression, which also include self-harm, poor bonding and poor parenting. SSRIs available in the US for treatment of depression include citalopram (*Celexa*, and others), escitalopram *(Lexapro)*, fluoxetine (*Prozac*, and others), paroxetine (*Paxil*, and others) and sertraline *(Zoloft)*.

FIRST-TRIMESTER USE — A case-control study in 9622 infants with major birth defects and 4092 controls found no significant association between use of SSRIs in early pregnancy and birth defects, except for a slightly increased incidence of anencephaly, craniosynostosis and omphalocele.[2] A similar study comparing 9849 infants who had birth defects with 5860 controls found no significant association between SSRI use in the first trimester and craniosynostosis, omphalocele or heart defects, but analyses of individual SSRIs found that use of sertraline was associated with septal defects and omphaloceles, and use of paroxetine was associated with right ventricular outflow tract obstruction.[3] Positive findings can occur by chance in malformation studies when multiple comparisons are made, and in both of these studies the absolute risks of all of these defects were small.

Other studies also found an increased risk of cardiac defects associated with paroxetine use in early pregnancy, leading the FDA and Health Canada to warn against such use, and the FDA to classify the drug as category D (positive evidence of risk) for use during pregnancy. One case-control study, however, found that the increased risk of major cardiac malformations with paroxetine use in the first trimester was statistically significant only in women who took more than 25 mg per day (the usual dose is 20 mg per day); for these women, the adjusted odds ratio was 3.07, with a 95% confidence interval that extended from 1.00 to 9.42.[4] A study of 1174 first-trimester exposures to paroxetine ascertained from 8 teratology information services found that the risk of congenital cardiovascular defects was no greater than in a comparison group of unexposed women.[5]

THIRD-TRIMESTER USE — Infants born to mothers who took an SSRI in the third trimester have been reported to have a higher risk of requiring treatment in an intensive care unit, possibly related to a withdrawal reaction, and of developing persistent pulmonary hypertension.[6,7] The possible neonatal withdrawal syndrome, which has usually been limited to feeding problems and jitteriness, but rarely has included convulsions and respiratory distress requiring intubation, has been associated particularly with paroxetine, which has the shortest half-life of the SSRIs.[8-10]

Persistent pulmonary hypertension, which occurs in 2 per 1000 live births, occurs in about one per 100 newborns exposed to an SSRI in the second half of pregnancy, possibly related to serotonin-related effects on cardiovascular development.[11] Persistent pulmonary hypertension can have serious consequences, including neurodevelopmental abnormalities and death.[12]

NEUROBEHAVIORAL DEVELOPMENT — Animals – Studies in rodent models have shown that increased extracellular serotonin concentrations can have adverse effects on the developing brain and cause changes in behavior, such as aggression, anxiety and depression, that may not become apparent until adulthood.[13] `

Humans – One study from an information and counseling program for pregnant women compared the children of 55 mothers exposed to fluoxetine during pregnancy (one third of the women took the drug throughout pregnancy) with the children of 84 mothers who did not take an SSRI during pregnancy and were not depressed. The children were tested,

apparently once each, between the ages of 16 and 86 months (mean age at testing 33 months). There were no significant differences between the 2 groups in IQ or language development.[14]

A second study from the same program compared 40 mother-child pairs (including 18 that were in the first study) exposed to fluoxetine throughout pregnancy to 36 mothers who were not depressed and not treated and their children. Neurobehavioral testing of the children between 15 and 71 months (mean age of the exposed children at the time of evaluation was 28 months and that of the control children was 42 months) found no significant differences between the 2 groups in tests of cognition, language and temperament.[15]

A small study that followed infants to 40 months of age found that treatment with SSRIs during pregnancy was associated with subtle effects on the motor development of the offspring, such as tremulousness and inappropriate fine motor movements; the control group consisted of women who were also depressed but did not take medication.[16]

There are no studies available following children exposed to an SSRI during fetal development into adolescence.

CONCLUSION — SSRI use during the first trimester of pregnancy generally appears to have a low risk of causing congenital abnormalities, but the risk of cardiac abnormalities with paroxetine is unclear. Third trimester SSRI use can cause apparent withdrawal symptoms and persistent pulmonary hypertension in the offspring. The long-term effects of SSRI exposure during pregnancy on neurobehavioral development are unknown. The potential risks of exposure to SSRIs during pregnancy must be weighed against the risks of untreated depression. □

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