Canterbury District Health Board
Te Poari Hauora ō Waitaha

# Clinical Pharmacology Bulletin

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## Neonatal outcomes after antidepressant use in the third trimester of pregnancy

Depression affects approximately 10% of pregnant women and is associated with adverse maternal and foetal outcomes. A previous bulletin (February 2012) discussed the potential risks associated with the use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs) in pregnancy. This bulletin will focus on neonatal outcomes after third trimester use of therapeutic doses of the same antidepressants.

**Birth outcomes:** The majority of data support an association of antidepressants with preterm birth. However, this effect is modest (shortens gestation by up to one week).

There are conflicting data regarding whether antidepressants cause reduced birth weight for gestational age. Two prospective studies that controlled for confounders (depression, smoking, maternal age and maternal weight) found no difference in birth weight between the exposed and non-exposed groups. Where studies support an increased risk of reduced birth weight for gestational age, the absolute difference is very small.

To date, antidepressant use does not appear to be associated with late obstetric loss (stillbirth).

**Poor neonatal adaptation:** The evidence strongly suggests that SSRI use during late pregnancy is associated with a cluster of neonatal signs, called 'poor neonatal adaptation'. This includes tachypnoea, hypoglycaemia, temperature instability, irritability, a weak or absent cry, seizures, respiratory distress and low APGAR* scores.

The mechanism is unclear. It may be the result of pharmacological toxicity, a 'withdrawal' or 'discontinuation' syndrome, or some other mechanism. The data suggests that neonatal adaptation difficulties following third trimester exposure to SNRIs are similar to SSRIs, although fewer exposed neonates have been studied.

Poor neonatal adaptation occurs in 15-30% of neonates exposed to SSRIs/SNRIs. Typically, signs are mild and begin during the first day of life, resolving within two weeks of birth. One prospective cohort reported a 100% incidence of 'neurobehavioural signs' in preterm (<37 weeks, n = 21) newborns (versus 69% for term babies, n = 55). In this study, the infants with 'neurobehavioural signs' had resolution of 75% of these within three or five days, for term and preterm newborns, respectively. The median length of hospital stay was 4-fold greater in SSRI- or SNRI-exposed preterm newborns, versus non-exposed preterm newborns.

The data for TCAs are less robust (case reports/series only). Infants with 'neonatal adaptation difficulties' following third trimester exposure to TCAs have been reported. Signs are drowsiness, jitteriness, hyperexcitability and rarely, convulsions.

**Bleeding:** We are aware of four case reports describing intracerebral haemorrhage in neonates after maternal SSRI treatment. This association with SSRIs and SNRIs is plausible as both decrease platelet serotonin and therefore decrease platelet aggregation. However, it is unclear whether the risk of this complication is higher than with non-exposed neonates. Intracranial haemorrhage is not uncommon in very premature/low birth weight infants who have not been exposed to antidepressants (incidence 60-70% in 500-750g neonates; 10-20% in 1000-1500g neonates).

**Persistent pulmonary hypertension of the newborn (PPHN):** SSRIs (and probably SNRIs, although there are less data) have been associated with an increased risk of PPHN when used in the second half of pregnancy (>20 weeks gestation). PPHN is associated with considerable morbidity and mortality. While the evidence from the three studies to date is not conclusive, it suggests that an increased risk is probable, but small (less than 0.5%). PPHN of the newborn is very rare, so the number of newborns affected is very small in absolute terms. Overall, the increased risk of PPHN is generally not considered sufficient to contraindicate use of SSRIs or SNRIs in the second half of pregnancy. TCAs have not been associated with PPHN.

**Developmental outcomes:** While there are only a small number of studies to date, it is reassuring that the majority report no developmental differences between infants exposed to antidepressants in-utero compared with those who were not.

**Limitations of the available data:** It is important to note that most studies assessing neonatal outcomes following antidepressant use in the third trimester have been observational. It is not clear to what extent the adverse effects observed in some studies are attributable to drug effect, versus maternal depression and/or other underlying maternal disease and/or other possible confounders.

**Risks of untreated maternal depression:** Infants born to mothers with untreated depression have an increased risk of irritability, reduced activity and attentiveness, poor maternal-infant attachment, inadequate nutrition, and poorer long-term developmental outcomes.

**Recommendations:** The treatment of depression during the third trimester of pregnancy is a risk versus benefit decision, where benefits often outweigh risks. Consideration should be given to providing a setting for delivery that can support neonates effectively following maternal antidepressant use during pregnancy. This is particularly so when there are other risks factors for prematurity and/or maternal antidepressant doses are high.

*APGAR = **A**ppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration score; designed to quickly assess a newborn's physical condition.

The information contained within this bulletin is provided on the understanding that although it may be used to assist in your final clinical decision, the Clinical Pharmacology Department at Christchurch Hospital does not accept any responsibility for such decisions.