Canterbury District Health Board
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Clinical Pharmacology Bulletin

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Antidepressant Use in Pregnancy – Part 2

Depression affects approximately 10% of pregnant women and is associated with adverse maternal and foetal outcomes. The decision to use or continue antidepressants in pregnancy centres around the risks to the mother and baby of untreated maternal depression, the effectiveness of non-pharmacological therapies and the risks associated with the use of antidepressants in pregnancy. Individualised treatment is key. This is the second of two bulletins which aim to discuss the potential risks associated with the use of the selective serotonin reuptake inhibitors (SSRIs), venlafaxine and mirtazapine in pregnancy.

Gestational hypertension

Women taking antidepressants during pregnancy may have an increased chance of gestational hypertension. Numbers needed to harm, from separate studies, have been estimated at 83 (for hypertension) and 40 (for pre-eclampsia) respectively. However, some studies have shown the association is related to maternal depression and anxiety. The association is particularly seen with venlafaxine and tricyclic antidepressants. One study found venlafaxine (but not SSRI) use from the 20th week of pregnancy to be associated with a significant increased risk of gestational hypertension; odds ratio 2.57 (1.34-4.93). Post-hoc analysis also showed higher doses of venlafaxine were associated with a risk similar to that recorded from psychostimulant exposure.

Bleeding and post-partum haemorrhage

SSRIs and venlafaxine are occasionally associated with bruising and bleeding, probably due to their serotonergic effects interfering with platelet aggregation. We are aware of four case reports describing intracerebral haemorrhage in neonates after maternal SSRI treatment. However, it is unclear whether the risk of this complication is higher in exposed compared to 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 500-750 g neonates; 10-20% in 1000-1500 g neonates).

Maternal antidepressant use close to term may cause a small increased risk of post-partum haemorrhage, possibly from serotonin-mediated reduction in uterine contractions and antiplatelet effects. A recent study found late pregnancy use of SSRIs, venlafaxine and mirtazapine increases the risk of post-partum haemorrhage. After adjusting for maternal mental illness the authors estimated a number needed to harm of 80 for SSRIs and venlafaxine, and 97 for less serotonergic drugs like mirtazapine.

Delayed neonatal adaptation syndrome (DNAS)

The evidence strongly suggests that SSRIs, venlafaxine and mirtazapine use during late pregnancy can cause a cluster of neonatal signs. DNAS occurs in 15-30% of neonates exposed to antidepressants and is most commonly described with fluoxetine, paroxetine and venlafaxine. Symptoms are usually mild and self-limiting (in the absence of polypharmacy), beginning during the first day of life and resolving within two weeks. DNAS is not associated with an increase in infant mortality. Common symptoms include:

- Irritability/drowsiness/restlessness
- Motor tone disorders/tremors/hyperreflexia
- Nasal congestion/tachypnoea
- Vomiting/diarrhoea/suckling difficulties
- Excessive crying (occasionally)

Hypoglycaemia, temperature instability, and seizures are rare occurrences. SSRIs have also been associated with a reduced APGAR score at 1 and 5 minutes of -0.4 to -0.2, which is of questionable clinical significance. Third trimester SSRI-exposed neonates have a two-fold increase in admission rates to neonatal intensive care units; however, maternal disease severity strongly contributes to this association.

The mechanism of DNAS is unclear but is thought to be from pharmacological toxicity, neonatal discontinuation syndrome, pre-term birth or a combination of these. Although the best treatment is not known, symptomatic and supportive therapies such as establishing breastfeeding, gentle or minimal handling, mother to baby direct skin contact and feeding on demand are suggested. One study found DNAS occurred more commonly in women who did not breastfeed. There is no evidence tapering or stopping antidepressants before birth reduces the risk of DNAS, and may leave the mother with no antidepressant cover at a vulnerable time

Persistent pulmonary hypertension of the newborn (PPHN)

PPHN is a rare cardiopulmonary disease that affects approximately 0.2% of neonates, with a mortality of 10-20%. When used in the second half of pregnancy (>20 weeks gestation), SSRIs and venlafaxine have been shown to double the risk of PPHN although the results of the various studies are conflicting. PPHN has also been associated with preterm birth, congenital malformations, caesarean section, maternal smoking, diabetes and obesity and aspiration of meconium. If there is an association with SSRIs or venlafaxine, the absolute risk appears to be small (2 to 3 neonates per 1000 of the general population).

Child neurodevelopment and long-term risks

The effect of *in utero* exposure to antidepressants on foetal brain development has been a concern for many years. While there are only a small number of studies to date, the evidence so far is reassuring. The majority of studies show no significant developmental differences up to the age of 6 years between children exposed to SSRIs *in utero* compared to non-exposed children with respect to mood, temperament, intelligence or cognition. Longer follow-up studies and adjustment for maternal mental illness, particularly post-partum depression, are needed. Post-partum depression is a significant risk factor for deficits in child language and intellectual development.

<u>Autistic spectrum disorders (ASDs)</u>

Recently there have been several studies published associating ASDs in children born to mothers who took SSRIs during pregnancy. Equally, there are studies showing no association following SSRI use, especially when other factors such as maternal illness and family environment are considered. Serotonin, hyperserotonaemia and variations in the expression of the serotonin transporter in children have been linked to ASDs. Theoretically exposure to antidepressants in early life may cause a 'high serotonergic tone" later in life. However, this serotonergic tone can also be affected by genetic factors and maternal chronic stress. Importantly, the prevalence of ASDs has been increasing in recent decades, and this increase started before SSRIs were marketed. If there is an association it has been estimated that antidepressant use in pregnancy could only account for <3% of ASD cases.