

GUIDELINES FOR

The use of SSRIs in pregnant women

One of the key considerations in managing antenatal depression is the safety of therapy for the fetus. All psychotropic medications pass through the placenta into fetal circulation in varying degrees. As such, the fetus will be exposed to these medications. These concerns—as well as the stigma of depression—are likely to be significant contributors to women's low likelihood of recognising depression at this time and reluctance to take medication.¹ Recent press and drug company releases about potential teratogenicity and withdrawal are likely to add to this anxiety. However, the quality of the evidence is generally poor, causal relationships often not proven and little long-term follow-up data collected. Selective serotonin reuptake inhibitors (SSRIs) are now increasingly used as first-line treatment for both depression and anxiety disorders; they are efficacious, better tolerated and safer than other classes for the mother, particularly tricyclics that are lethal in overdose. This article summarises the information that needs consideration by the treating clinician, the woman and her partner in deciding about treatment with SSRIs in pregnancy.

First trimester

For many women, pregnancy is not planned. If they are taking medication, by the time of pregnancy confirmation a significant exposure has already occurred. This discovery can prompt immediate cessation through fear of teratogenicity even before the woman has visited her doctor, increasing risks of withdrawal and relapse.²

Ideally, it would best to avoid infant exposure to any medication. If the woman has only had one episode, has been well for two years and is in a non-stressful environment, with cognitive therapy techniques, regular yoga or exercise, the decision to gradually withdraw medication and have up to a year well and medication-free, is fairly straightforward.

When the woman has had a more severe and recent depression, this decision is a balance—one where the clinician's role is to provide information and allow the woman and her partner to make an informed decision.

There have been a number of studies on Fluoxetine³⁻⁵ with a majority showing no fetal abnormalities and one citing a slight increased risk of minor malformations.³ However, a more recent study,⁶ showed SSRI exposure increased risk of omphalocele (Paroxetine in particular) and craniosynostosis. GlaxoSmithKline (GSK) in their own study also found associations of Paroxetine and cardiovascular malformations (OR 2.08.95 per cent CI 1.03 – 4.23). Suggestions of an increased link with risk of miscarriage have also been reported in some studies with Fluoxetine⁴ but not replicated by other researchers.⁷

Less is available on other commonly used SSRIs, with some disparity, but current knowledge studies suggest less risk of teratogenicity with other SSRIs such as Sertraline, Citalopram and Fluvoxamine.

Second and third trimester

Fluoxetine in one large study was associated with an increased risk of significant prematurity.³ The premature infant is less able to metabolise the drug, particularly if it is exposed to ongoing medication through breast milk. The long half-life of Fluoxetine may also be problematic for these infants.

There have been no consistent reports of other antidepressants being associated with prematurity.

Where the woman has not delivered prematurely the ability to metabolise still needs consideration. Planning the day of delivery can have the advantage of enabling medication to be decreased or ceased briefly in the few days before the induction, reducing fetal blood levels, but this increases the risk of relapse and is probably not ideal in those with severe illness.

Throughout pregnancy and delivery

Whilst the data on malformations suggests the safety of antidepressants, the effect of the exposure on more subtle neurological development remains uncertain. Whether there is any particular time of heightened exposure risk and whether dosage is important are also unknown.

One study has looked at different placental blood transfers (via cord blood at birth) of two

ANNE BUIST
MD FRANZCP

ASSOCIATE PROFESSOR OF
PSYCHIATRY
UNIVERSITY OF MELBOURNE

DIRECTOR
BEYONDBLUE NATIONAL
PND PROGRAM

DIRECTOR, BANKSIA HOUSE
MOTHER BABY UNIT,
AUSTIN HEALTH
& THE NORTHPARK
MOTHER BABY DAY
PROGRAM

MELBOURNE, VIC

antidepressants, Fluoxetine and Sertraline, and concluded that there are significant differences, with the infant being exposed to more Fluoxetine.⁸

Zeskind and Stephens⁹ studied the infants of women exposed to SSRIs in pregnancy and compared them with the infants of women who had not taken these drugs. They found significant differences with SSRI-exposed infants with respect to tremulous and sleep and other effects on motor activity, but also noted that there was no increase in malformations and that these infants were healthy and full birth-weight newborns. This study assumed all SSRIs can be lumped together as one when they have significantly different properties and does not compare infants of depressed mothers who have been noted to have had negative effects from the depression, separate from any medication.¹⁰⁻¹²

Other studies also describe irritability, heightened reactivity and difficulties settling after delivery.¹³ Barclay¹⁴ reported on neonates exposed to Paroxetine in third trimester and found an increased risk of complications. These appear to be short-lived and it is unclear whether or not they are side effects or longer-term developmental effects. The relevance of these findings and whether they normalise has not been established but does appear to represent a withdrawal syndrome.

Longer term follow-up has been inadequate. In Heikkinen *et al's*¹⁵ small study they conclude infants exposed to Citalopram were neuro-developmentally normal at one year. In two other reports^{16,17} one prospective study of tricyclics and Fluoxetine were seen to not adversely affect IQ or behaviour at 15-86 months.

Effect of maternal anxiety and depression

The concerns and unknowns of medication need to be balanced with the data available on the effects of maternal anxiety and depression on the infant both *in utero* and postpartum—potentially heightened if untreated (see Table 1). Of note, maternal suicide is the equal leading cause of maternal deaths in Australia,¹⁸ so assessment of severity of depression is essential.

Depression and anxiety *in utero* have been associated with changes in fetal blood flow and corticosteroid levels in the infant at birth.¹⁹ One possible long-term effect of this might be to sensitise the infant to later depression and anxiety.²⁰

Considerably more studies have examined the effects of postpartum depression on infant and child development including cognitive delays, behavioural disturbance and potential anxiety and depression.¹¹ Whilst studies showing that treating perinatal depression improves outcomes for the child are inadequate, early and assertive treatment is current best practice until a more specific treatment is developed and evaluated.

Conclusions

In an era of increased awareness of patient rights and medico-legal angst, treating pregnant women for depression with antidepressants is a source of concern for both mothers and clinicians.

Untreated depression has a personal cost as well as a risk of suicide. Perinatally there is the risk to the infant—with evidence pointing towards a significant risk—from biological effects of maternal anxiety on the fetus and from the long-term negative impacts of maternal depression on development.

This needs to be balanced against the risk of the treatment to the fetus, summarised in Table 1.

Table 1

Risks of not treating	
<p>Mother</p> <p>Worsening depression with risk of:</p> <ul style="list-style-type: none"> • Poor self esteem • Inability to work • Marital tension/ break up 	<p>Fetus</p> <p>Increased exposure to high cortisol with later increased risk of:</p> <ul style="list-style-type: none"> • Educational difficulties • Poor self esteem • Anxiety • Depression
Risks of treating	
<p>Mother</p> <p>Side effects of medication</p>	<p>Fetus</p> <ol style="list-style-type: none"> 1. First trimester teratogenicity <ul style="list-style-type: none"> • Paroxetine • Possibly others - inadequate data 2. Prematurity <ul style="list-style-type: none"> • Fluoxetine 3. Withdrawal at delivery <ul style="list-style-type: none"> • All, but possibly worse with Paroxetine

If the illness is moderate to severe and is unresponsive to other treatments then antidepressants should be considered and discussed. The studies are currently still inadequate, but suggest that in using an SSRI, Paroxetine should—if at all possible—be avoided. Less is known about selective norepinephrine re-uptake inhibitors (SNRIs) eg, Venlafaxine.

Whilst a number of factors will influence the choice of antidepressant, current best evidence for minimising risk to infant suggests tricyclics, Sertraline, Citalopram and Fluvoxamine to be the drugs of first choice.

Whatever antidepressant is selected the pregnancy/infant should be monitored closely and may require paediatric assessment and a longer period of observation in hospital. For future pregnancies, careful forward planning is recommended.

2006 RANZCOG Workforce Survey

February 2006

Workforce surveys provide the College with valuable data on the changing O&G workforce. Since 1997 the College has surveyed the Fellowship every three years to gain a snapshot of the O&G profession.

The 2003 Workforce Survey was conducted at a time of serious concerns regarding medical indemnity. The results indicated that a significant number of Fellows intended to cease practising private obstetrics and to a lesser extent public obstetrics. The 2006 Survey will enable the College to gather data on the extent to which this intention to cease obstetrics was implemented. Once again, the Survey will be conducted in uncertain times, with the potential for significant change as a result of the recent report from the Productivity Commission.

The 2006 Workforce Survey will, for the first time, include all Trainees. In 2001 5th and 6th year Trainees and new Fellows were surveyed to find out their practice intentions: it was of concern to the College to find that 26 per cent of those surveyed had no intention of ever practising obstetrics.

The 2006 Workforce Survey will be distributed by mail in **February 2006** and all Fellows and Trainees are requested to look out for it and respond promptly. Like the Fellows Feedback Survey (2004), it will also be possible to complete the 2006 Workforce Survey **online**.

The 2006 Workforce Survey will be managed by a working party of Councillors and Fellows and administered by Australian Survey Research (ASR).

For further information please contact:

Valerie Jenkins
RANZCOG Fellowship Services Manager
(t) +61 3 9412 2948
(e) vjenkins@ranzco.org.edu.au

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