Psychotropic Medication in Pregnancy/Lactation

2nd Edition

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General Points:
None of the Psychotropic medications have been thoroughly studied with regards to
risks in pregnancy and lactation. Most evidence consists of case reports, small studies
and a few population based Birth Registry Studies and retrospective case-controlled
studies. There are limited numbers of small prospective cohort studies and virtually
no blinded placebo RCTs. Therefore studies are NHMRC level III evidence or below.

The risks can be conceptualised as:

a) those for the mother, including side effects of the medication and also risk of
deterioration / relapse without the medication.

b) the risks to the fetus and infant from exposure to the medication, but also from
having an unwell / untreated mother.

Psychotropic medication prescribed during pregnancy may compromise an
infant through:

a) Teratogenicity (malformation)

b) Pregnancy complications (e.g. miscarriage, prematurity, low birth weight,
   inducing maternal diabetes etc.)

c) Neonatal complications (e.g. withdrawal syndromes, sedation, persistent
   newborn pulmonary hypertension etc.)

d) Longer term complications (e.g. neurobehavioural disturbance,
   neurodevelopmental outcomes etc.)

The evidence that is emerging on the long term effects of untreated maternal
psychopathology on infant development is convincing (e.g. I.U.G.R., prematurity, lower
birth weight, smaller head circumference, lower APGAR scores, and HPA dysfunction
possibly leading to an increased risk of psychopathology later in life, developmental
delay, or later disturbance in the areas of cognitive, emotional and social functioning
etc.), however this has to be balanced against the mostly unknown long term effects of
early exposure to psychotropic medication either in-utero or via excretion in breast milk.
In addition, it should be noted that women with major depression who cease their
antidepressants in pregnancy have a 50-75% risk of relapse, and even higher for those
with bipolar disorder who cease their medication.
When giving advice on psychotropic use in pregnancy/lactation it is important to remember that psychotropic medication is usually used in the long term, that is for the duration of the pregnancy or period of breast-feeding. They are not usually given for a short period, such as antibiotics or other medications used for women during this period. In addition, most psychotropic medications such as antipsychotic medication and antidepressants are given once daily as they reach a steady state in plasma and breast milk. Thus discarding of breast milk or timing feeding around medication is not advised as it is thought to make little difference to the dose received by the infant.

Due to changes in gastric emptying, increased volume of distribution, decreased GI motility, decreased drug binding capacity and increased hepatic metabolism during pregnancy there is a need to monitor the dose of the psychotropic medication carefully.

All psychotropic medications are excreted into breast milk and in general most may cause sedation of the infant, which manifests as poor feeding. Infants of mothers on such medications require careful monitoring of behaviour and growth by experienced clinicians. There is a notional safety limit of a relative infant dose of under 10% of the maternal dose, which can be used to understand data around breast milk excretion. However, it must be noted that premature infants and infants less than 6 months of age have immature livers and hepatic metabolic systems. It is advisable to have a much higher threshold for the use of psychotropic medications in this group.

At least 50% of pregnancies are unplanned and many women may not realise that they are pregnant until well into their first trimester. Commonly psychotropic medications are abruptly withdrawn in an attempt to protect the developing fetus from drug exposure. However, many medications are associated with a discontinuation syndrome that, in itself, could compromise a pregnancy, and relapse rates of underlying psychiatric conditions also tend to be high.

The basic principle for all patients involves the provision of full information to the patient (and, where appropriate, the husband or partner) so they are able to make an informed decision, balancing the risks and benefits for each individual.

1. Serotonin Selective Re-Uptake Inhibitors

Pregnancy (Risk Category C, Paroxetine Risk Category D)
- Probably safe in terms of teratogenicity, other than Paroxetine that is possibly associated with a higher rate of cardiac malformation with exposure in 1st trimester, and Fluoxetine that is possibly associated with higher rates of minor anomalies.
- Slightly higher incidence of miscarriage, but underlying condition could also be a contributing factor. No differences were seen with different antidepressant classes.
- Associated with lower birth weight and prematurity.
- Possibility of increased risk of Persistent Pulmonary Hypertension of the Newborn (PPHN) following late pregnancy SSRI use. As the condition is rare, the absolute risk is thought to be low. In one study the population risk of 4:1000 deliveries was increased to 12:1000 deliveries. However, PPHN is a serious condition with 10-20% mortality and potentially substantial morbidity.
- Discontinuation Syndrome: use in late pregnancy has been associated with increased rates of admission to NICU and SCN of neonates with a range of difficulties including sleep, feeding and breathing difficulties, jitteriness, tremors, irritability, hypotonia, poor temperature control, and gastrointestinal symptoms. It is unclear if this is due to withdrawal or serotonin toxicity. Most are mild and transient with no long term sequelae reported in the small number of available follow-up studies. There is no specific treatment, however paediatric monitoring and admission, if required, is recommended. The risk seems higher with those SSRIs with a shorter half life, and those with greater placental passage.
- Although this has not been studied, some clinicians recommend reducing the dose one week prior to delivery, and then increasing again at delivery in order to potentially reduce the risk of neonatal complications. However, this needs to be carefully balanced against risk of deterioration in the condition being treated during an already high-risk period. It should also be noted that due to physiological changes in late pregnancy, it is likely that previously therapeutic dose will be less effective.
- Placental Passage: Lowest in Sertraline and Highest in Citalopram and Fluoxetine.
Lactation
- Probably safe.
- Low levels excreted for most SSRIs.
- Relative infant doses: a relative infant dose of lower than 10% of the weight adjusted maternal dose is considered to be safe for breastfeeding.
- Relative Infant Doses: Sertraline 2.2%, Citalopram & Escitalopram 3.6%, Paroxetine 2.1%, Fluvoxamine 1.3%, Fluoxetine 6.8%.
- Some concern with Fluoxetine given its long half life and the risk of accumulation in the infant.

Suggestions
- Preference should be given to Sertraline whenever appropriate due to its demonstrably lower placental passage, minimal excretion in breast milk, and lower likelihood of producing withdrawal states in the newborn.
- Infants exposed to SSRIs in late pregnancy should be monitored until day 3-5 for a discontinuation syndrome. Given the possible risks of late pregnancy exposure, paediatric staff should be involved in early postpartum care.

2. Tricyclic Antidepressants

Pregnancy (Risk Category C)
- Probably safe, miscarriage rate as per SSRIs.
- Observe for sedation, withdrawal states, and other forms of neonatal compromise.
- Careful consideration must be give to assessment of maternal suicide risk given the potential lethality of tricyclic antidepressant overdose.
- There may be some benefit in reducing the dose one week prior to delivery.
- And increasing again at delivery in order to reduce the risk of neonatal complications. However, this needs to be carefully balanced against risk of deterioration in the condition being treated during an already high-risk period.

Lactation
Probably safe: low levels excreted for most tricyclics. Relative infant doses:
- Amitryptiline 1.5%, Clomipramine 2.8%, Dothiepin 4.4%, Doxepin 1.2%, Imipramine 0.15%, Nortriptyline 1.5%.
- Avoid Doxepin if possible due to reported risk of dangerous sedation, respiratory arrest and poor sucking.
- Monitor all infants closely for sedation.

3. MAOIs

Pregnancy (Risk Category B)
- Phenelzine & Tranylcypromine associated with teratogenicity, therefore use as last line.
- Limited data regarding Moclobemide.

Lactation
- Phenelzine & Tranylcypromine: no reports of use during lactation. Use with extreme caution.
- Moclobemide probably safe. Relative infant dose 3.4%.

4. Mirtazapine, Venlafaxine, Mianserin, Reboxetine & Bupropion

Pregnancy (Risk Category B)
- Unknown risk, little human data.
- Venlafaxine was not associated with any major malformations in one study, but has been associated with higher risk of neonatal complications including neonatal withdrawal and convulsions.
- Limited case studies of Mirtazepine exposure in pregnancy have not shown it to be associated with major malformations. One study has found that Mirtazepine may be associated with higher rates of prematurity and lower rates of live births compared with controls, but the rates were similar to SSRIs and tricyclics.

Lactation
- Little evidence for all except Venlafaxine and Mirtazapine. Studies for these are small Relative infant doses are 6.4% and 1.9% respectively.

5. Electro Convulsive Therapy

Pregnancy
- Can be associated with premature labour, adverse effects in infants rarely seen.
- Recommendations: Obstetric consultation (with pelvic examination prior to ECT), Fetal Heart Monitoring and Intubation (beyond first trimester).

Lactation
- Probably safe. Liaise with anaesthetic staff about risks associated with anaesthetic agents.
6. Lithium

Pregnancy (Risk Category D)
- Risk of Ebstein’s Anomaly 0.05-0.1% (much lower than previously reported).
- High serum levels of lithium during pregnancy have been associated with polyhydramnios and foetal macrosomia.
- Risk of prematurity and large-for-gestation infants also reported.
- No evidence of long term neurodevelopmental toxicity.
- Transient withdrawal states, hypotonia, hypothyroidism and nephrogenic diabetes has been observed.

Suggestions
- Avoid in first trimester if possible.
- Monthly monitoring of lithium level until final month, then weekly.
- Will probably require higher dose in last trimester due to increased GFR/plasma volume. Dose should be given in three to five equal doses per day of no more than 300mg per dose measured against risk of poor compliance with multiple dosing.
- High resolution echocardiography, foetal echocardiography and Doppler flow studies recommended around 16-18 weeks gestation.
- In final 10 days of pregnancy gradually taper dose by approximately 30%.
- Risk of relapse post partum is approximately 20-50%, so ongoing close monitoring is required.
- Monitor TFT closely as can affect if the mother becomes hypothyroid.
- At delivery ensure adequate hydration and monitor closely for lithium toxicity, as this can occur in the context of the normal peri-partum diuresis and dehydration associated with delivery. Avoid co-administration of medications that may increase the risk of toxicity (e.g. ACE inhibitors, Calcium Channel Blockers, Diuretics, and NSAIDs).

Lactation
- Potentially hazardous as breast milk contains 30-50% of maternal serum level.
- Neonates are far more sensitive than adults.
- Use with caution only if no other option and infant must be referred to a paediatrician for regular monitoring of lithium levels and thyroid function.
- Note lithium does not reach steady state until day 10 so effects are not seen in the early peri-partum period.

7. Sodium Valproate

Pregnancy: (Risk Category D)
- 1-3% risk of neural tube defect. Incidence of major malformation is approximately 11% (in one study up to 16%).
- Risk of malformations and complications greater when doses above 1000mg per day used.
- Fetal Valproate Syndrome: a pattern of cardiac, facial and central nervous system anomalies and intrauterine growth restriction.
- Valproate exposure also associated with I.U.G.R., minor abnormalities such as changes in facial features, fingers, toes and abnormal liver function. Major abnormalities such as reduced cranial size associated with lower intelligence, cognitive dysfunction and oral clefts, hepatotoxicity, and hypoglycaemia are also associated.
- Developmental delay has been associated with exposure.
- Overall rate of 5-15% risk of associated complications and the odds ratio for major abnormality almost doubles when two or more anti-epileptic drugs are taken.
- Sodium valproate serum level decreases in mother after second trimester, however foetal levels increase.

Suggestions
- Use only when absolutely necessary.
- Aim for doses below 1000mg daily and avoid combining anti-epileptics.

Lactation
- Generally considered low risk.
- Relative infant dose 0.68%.
- Observation of infant for liver enzyme and platelet dysfunction advisable.
8. Carbamazepine

Pregnancy (Risk Category D)
- Risk of neural tube defects 0.5-1%, especially in doses higher than 1200mg/day. Overall incidence of foetal malformation is 5.7%.
- Lower than 2% risk of major congenital malformation (kinked ribs, cleft palate, anophthalmos, I.U.G.R.)
- Associated with neonatal hepatotoxicity and developmental disability.
- Coagulation defects with consequent risk of haemorrhage in the foetus and the neonate, which may be preventable by the prophylactic administration of vitamin K to the mother prior to delivery.

Lactation
- Generally considered low risk other than a slight concern regarding neonatal jaundice.
- Relative infant dose 4.35%.

9. Lamotrigine

Pregnancy (Risk Category D)
- Limited data suggests probably safe. No increased rate of major congenital malformation, however risk is likely to be dose related.
- Plasma concentrations may reduce during pregnancy, possibly requiring increased doses with dose reduction following delivery.
- Associated with neonatal hepatotoxicity.

Lactation
- Currently considered moderately safe.
- Breast feed with caution due to high milk: serum ratio. Relative infant dose 22.7%.
- Theoretical concern about Stevens Johnson Syndrome – potentially life threatening rash.

Overall Recommendations for Mood Stabilisers

Pregnancy
- Avoid, if possible, medications during period of organogenesis. Taper medications; do not cease abruptly. Avoid multiple medications if possible.
- Malformation rate for the general population is 2-4% risks of medication exposure must be compared to this.
- If medication is required in pregnancy then the preference is: lithium, high potency neuroleptic medication, olanzapine or lamotrigine, preferably not carbamazepine or sodium valproate (highest teratogenic potential of mood stabilisers).
- Lithium used during second and third trimesters does not increase birth defects, but may be associated with pregnancy complications.
- For those who require anti-convulsants in pregnancy, prescribe high dose Folic Acid (5mg daily) prior to and throughout pregnancy (although advantage in preventing neural tube defects associated with antiepileptics is unclear).
- Detailed ultrasound and maternal alpha-fetoproteins or amniocentesis recommended at 12 weeks when anti-convulsants prescribed during pregnancy.

Lactation
- Sodium valproate safest, lithium only with extreme caution. Infant must always be observed for sedative effects such as poor feeding.
- Use of bromocriptine and cabergoline not recommended should lactation suppression be required due to increased risk of precipitating puerperal psychosis.

10. Antipsychotic Medication

Pregnancy (Risk Category C)
- More evidence regarding safety with typical, rather than with atypical anti-psychotics.
- Overall data regarding the safety of anti-psychotic medication during pregnancy is extremely limited; however that which is available suggests low risk.
- Anti-psychotic medication is generally used to treat significant mental illness and this needs to be considered when making a risk: benefit analysis.
- Strive for lowest therapeutic dose (esp. first trimester).
- Risk of prolonged neurological disturbance in the neonate (esp. sedation and extra pyramidal side effects).
- High-potency antipsychotics considered safest (eg. haloperidol), those with an aliphatic side chain (eg chlorpromazine, trifluoperazine) least safe. Watch blood pressure if chlorpromazine used.
11. Benzodiazepines

Pregnancy (Risk Category C)
- Risk of cleft palate (unclear, approximately 1% in some studies) in first trimester.
- Some concern with Clonazepam and excessive risk of teratogenicity.
- Risk of Floppy Infant Syndrome (hypotonia, respiratory depression and hypothermia) if used close to birth. This appears to be dose related.
- Benzodiazepines can also be associated with hyperbilirubinemia in the neonate and a withdrawal syndrome with prolonged use.
- Shorter acting agents considered safer.
- Avoid abrupt discontinuation: taper.

Lactation
- Generally considered moderately safe.
- Shorter acting agents such as oxazepam, alprazolam and temazepam preferred.
- Risk of accumulation with longer acting agents.
- Observe for sedation if used.

12. Zolpidem & Zopiclone

Pregnancy (Risk Category Unknown):
- Extremely limited data available – unable to assess safety.
- Potential for withdrawal state and CNS depression in the neonate.

Lactation
- Avoid due to limited safety data.
- Observe for infant sedation if used.

Lactation
- Some excretion occurs in all anti-psychotic medication, however data to date suggests that levels are low (generally less than 3% of maternal dose).
- Once again there is more evidence to suggest moderate safety with typical, when compared with atypical anti-psychotics, due to an extreme lack of data in the latter group. Longitudinal data lacking for all.
- A small study of Quetiapine found levels not detectable in breast milk in doses less than 75mg. Small studies on breast milk excretion in Olanzapine and Risperidone suggest levels less than 5%. Observe for sedation (especially poor feeding) if used.
- Pharmacological suppression of lactation: advice as per mood stabilisers.
- There is a risk of agranulocytosis with Clozapine. Breast milk excretion has varied in studies, some indicate low levels others have shown high concentrations. Therefore, the advice is to avoid breast feeding with clozapine.

Atypicals: There is only limited data available. Clozapine has been associated with an increased risk of gestational diabetes, floppy infant, seizures and gastroesophageal reflux. There appears to be a tendency for low birth weight and for admission to neonatal intensive care. The adverse pharmacological and toxicological effects of Clozapine in adults may also occur in the fetus/neonate such as agranulocytosis. Some studies suggest Olanzapine, Quetiapine and Risperidone are not associated with increase in congenital anomalies, reduced gestation or birth weight. Olanzapine is associated with increased risk of gestational diabetes. Aripiprazole: only case reports are available these have not suggested any congenital anomalies associated but this is extremely limited data. There is little data for Ziprasidone in pregnancy or lactation. Women on atypicals have been found to have an increased risk of neural tube defects. This is thought to be due to obesity and low folate levels.

Placental passage: One study has demonstrated highest levels with olanzapine (72.2%), then haloperidol (65.5%), then Risperidone (49.2%) and Quetiapine (23.8%).

Limited data regarding the use of anti-cholinergic medication, however there is a suggestion that there may be an increased risk of cardiovascular defects, therefore avoid if possible.

Lactation
- Some excretion occurs in all anti-psychotic medication, however data to date suggests that levels are low (generally less than 3% of maternal dose).
- Once again there is more evidence to suggest moderate safety with typical, when compared with atypical anti-psychotics, due to an extreme lack of data in the latter group. Longitudinal data lacking for all.
- A small study of Quetiapine found levels not detectable in breast milk in doses less than 75mg. Small studies on breast milk excretion in Olanzapine and Risperidone suggest levels less than 5%. Observe for sedation (especially poor feeding) if used.
- Pharmacological suppression of lactation: advice as per mood stabilisers.
- There is a risk of agranulocytosis with Clozapine. Breast milk excretion has varied in studies, some indicate low levels others have shown high concentrations. Therefore, the advice is to avoid breast feeding with clozapine.
The decision to start or continue psychotropic medication in pregnancy is a serious one. There must always be a risk/benefit analysis given the unknown risks for the exposed foetus. Where there is uncertainty, we recommend you seek expert advice.

Further Information
• Perinatal Psychiatry Unit, Mercy Hospital for Women, ph. (03) 8458-4834.
• Mercy Hospital for Women Drug Information, ph. (03) 8458-4674.
• Breast Feeding Support Unit, Mercy Hospital for Women, ph. (03) 8458-4677.
• Royal Women’s Hospital Drug Information, ph. (03) 9344 2000.
• Monash Medical Centre Drug Information, ph. (03) 9594 6666.
• Mental Health Research Institute Psychotropic Drug Information Service, ph. (03) 9388 1633.

Suggested References
• Colvin, J. The Royal Women’s Hospital Drugs and Breast-feeding Guide, Drug Information Centre, The Royal Women’s Hospital, Melbourne.