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Motherhood and mental illness

Part 2 – management and medications

Background
General practitioners see many women who may be on medication for the management of their mental illness before, during, or after a pregnancy.

Objective
This article reviews the current evidence and gives practical advice on management and use of psychotropic medication in women with mental health disorders in pregnancy.

Discussion
The general practitioner is often the first point of contact, and is vital in giving timely and accurate information and encouraging appropriate treatment choices in women with mental illness in our community. The risk-benefit analysis of treatment needs to be considered in light of the evidence at hand. Specialist opinion in complex cases must be sought early.

Choosing the right treatment for a pregnant or breastfeeding woman with a mood or anxiety disorder is a difficult task given the uncertainty surrounding the potential risks of medication. The common concern for many pregnant women is whether a medication will affect the development of their child, and in the absence of reassuring information, many will either forgo necessary pharmacotherapy or cease existing treatment, much to their own and that of their child's detriment. While one cannot afford to minimise the unknown, the clinician needs to emphasise to their patient that the decision to use medication or any form of treatment during the pregnancy and breastfeeding period should occur after a thorough risk-benefit analysis with specific attention to the needs of the individual. The adverse effects of failure to treat may be significant for both mother and child.

A good therapeutic relationship is needed in reassuring a woman to adhere to therapy, and general practitioners are in an ideal position to offer advice. However, the sequence of advice received may be important in the woman's decision making process, with the only determinants appearing to correlate with a final decision being the number of positive and negative sources received, and the initial risk perception.[1] It appears that risks are more worrying and less acceptable if they arise from a man made or unfamiliar source, and that 'natural' risks are better tolerated.[2] A discussion about teratogenicity from the medication, even if the risk is viewed as small in comparison to the risks of the untreated mental illness, may provoke concern in most expectant mothers.[3]

Treatment selection is influenced by:

- illness factors such as severity of symptoms
- relevant past history and effective treatments
- time interval between previous cessation of medication and relapse of the disorder and level of functioning in this interval
- the likelihood of compliance
- suicide risk
- the risks to the infant, including potential for neglect, and parental concerns around the medication, and financial and time

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constraints. It is important to consider both pharmacological and nonpharmacological approaches to the management of a woman with mental illness during the pregnancy and postpartum period.

Nonpharmacological management strategies

An individual treatment approach is advocated and selection is based on many criteria, including patient choice, financial considerations and past experience. Nonpharmacological therapies, such as cognitive behavioural therapy, have been shown to be effective for treatment of postnatal depression[4] and may have synergistic effects when combined with medication.

Various other nonpharmacological therapies have been used for mild to moderate depression (*Table 1*). Part 1 of this article outlines a range of important social and support strategies that are vital to good management (see *Australian Family Physician* August 2009 issue).

Table 1. Nonpharmacological strategies

- Supportive therapy
- Cognitive behaviour therapy
- Interpersonal psychotherapy
- Psychodynamic therapy
- Increased exercise
- Massage therapy
- Stress and relaxation therapies
- Relationship counselling or couples therapy
- Nutrition and dietary supplements (eg. omega 3 fatty acids)

Pharmacological management strategies

Medication during pregnancy

While a discussion on the management of specific disorders is beyond the scope of this article, we aim to examine the ever changing body of safety data available for the psychotropics, and to formulate treatment approaches. When assessing the risks and benefits of taking medication during pregnancy, women and their physicians should be aware that the abrupt discontinuation of psychotropic drugs might lead to serious adverse effects. It is also important to note the biological changes of pregnancy, such as changes to renal function, which will impact on the dosing of renally excreted agents such as lithium. *Table 2* outlines some basic general principles for the prescription of medications during pregnancy.[4] Due to the complexities involved in managing pregnant women who are taking antipsychotics or mood stabilisers, access to specialist care is important.

Table 2. General principles for use of medication[4]

- Medication should be avoided where possible, especially during the first trimester; however untreated mental illness also poses risks during this time
- Following consultation, an agreed plan, with appropriate input from the woman, her partner, the GP, the obstetrician and the psychiatrist, is followed
- If conception occurs unexpectedly, medication should not be withdrawn abruptly; medical guidance is necessary
- If medication is used an effective dose should be prescribed. Generally, the principle of 'start slow, go slow' applies
- Monotherapy up to therapeutic or higher doses is preferred over combination therapy
- If a medication has been effective in the past this should be the first choice
- Careful monitoring, especially during periods of change, is essential
- Adequate folic acid supplementation (5 mg) needs to be considered, especially with certain medication (eg. anticonvulsants)
- In patients with a history of severe mental illness, prophylaxis can be considered in late pregnancy
- Medication used in pregnancy should be continued postpartum
- Neonatal discontinuation symptoms are not uncommon, although rarely severe. The infant may need to be monitored closely for the first 5 days
- Information changes rapidly and it is important to keep up-to-date

Antidepressants

Tricyclic antidepressants have been used for many years. They have robust safety data but have a higher risk of side effects, including lethality in overdose. Due to their side effect profiles they are mainly used as second line agents in clinical practice at present.[5] The newer antidepressants consist of the selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and mirtazapine.

As a group, the SSRIs (with possibly the exception of paroxetine) are not associated with an increased risk of major malformations above the baseline of 1–3% in the population.[6,7] They have been associated with slightly increased rates of spontaneous abortion.[7,8] Prenatal antidepressant use is associated with lower gestational age at birth and an increased risk of preterm birth.[7,9,10] Many experts however, believe that these risks may be due to the depression itself. Delivery outcome after exposure to SNRIs and mirtazapine resembles that described after use of SSRIs.[7,8]

Exposure to SSRIs late in pregnancy is associated with an increased risk of the infant developing a constellation of symptoms often referred to as 'neonatal discontinuation syndrome'. These symptoms include central nervous system and respiratory effects, low Apgar score, myoclonic jerks, jitteriness, and restlessness and irritability, and may occasionally require observation and supportive or specific treatment in a neonatal special care nursery. For these

reasons, the opportunity of tapering and discontinuing SSRIs in late pregnancy should be taken into consideration; although to date, the evidence to support such a clinical decision is preliminary.[11] The signs resolve in 75% of cases within 3–5 days for term and premature newborns, respectively. Premature infants could be more susceptible to the effects of SSRIs and venlafaxine.[12] All SSRIs and SNRIs carry the risk of discontinuation syndrome in neonates, however it is important to emphasise that in most cases the effects are mild and self limiting. A recent concern relating to persistent pulmonary hypertension (PPHN) in the neonates of mothers taking antidepressants during their pregnancy may be less worrisome than first thought.[13]

Antipsychotics

Antipsychotics are the mainstay of treatment for psychotic disorders. There are two main groups:

- the older typical antipsychotics (eg. chlorpromazine, haloperidol, trifluoperazine), and
- the newer atypical antipsychotics (eg. risperidone, olanzapine, quetiapine).

While the atypical antipsychotic agents are more often used in treating psychosis due to their tolerability, there is a paucity of prospective studies into their safety in pregnancy, especially in the first trimester. Safety data often comes from retrospective studies and medication registries, which have their limitations. In 2005, a National Register of Antipsychotic Medications in Pregnancy was established in Australia and preliminary data appears encouraging.[14] Some authorities, such as the National Institute of Clinical Excellence in the United Kingdom, recommend a switch from atypical to typical antipsychotics such haloperidol, chlorpromazine or trifluoperazine, which have better safety data, if an antipsychotic is needed in the first trimester.[15] However, typical antipsychotics are not particularly effective in the treatment of bipolar affective disorder (BAD). Atypical antipsychotics such as olanzapine are associated with substantial body weight gain and may increase risk of gestational diabetes.[5,9] They may increase infant birth weight and the risk of large for gestational age infants.[16]

Mood stabilisers

Mood stabilisers such as lithium and anticonvulsants present major challenges in managing the pregnant woman with BAD. On the one hand there is a high risk of relapse of BAD if the mood stabiliser is discontinued,[17] and on the other hand, agents such as lithium and sodium valproate are highly problematic if used during pregnancy. Reported neonatal problems with maternal lithium therapy include:

- Ebstein anomaly (a congenital tricuspid valve abnormality)
- poor respiratory effort and cyanosis
- cardiac rhythm disturbances
- nephrogenic diabetes insipidus
- thyroid dysfunction
- hypoglycaemia

Table 3. Considerations in medication use – pregnancy and postpartum

Drug	Maternal	Fetal	Breastfeeding
Antidepressants			
• SSRIs – fluoxetine – sertaline – citalopram – escitalopram – paroxetine	• Discontinuation of medication increases risk of depression and anxiety • Associations with increased risk of miscarriage, intrauterine growth rate and preterm birth[22] may be related to the underlying condition	• Not associated with an increased risk of major malformations above the baseline[6] • Paroxetine best avoided in early pregnancy as conflicting studies of risk of fetal heart disease[23] • Exposure linked with transient neonatal discontinuation symptoms[12] • Possible association with PPHN less likely than thought[13]	• Low excretion in breast milk, compatible with breastfeeding • Most studies report few adverse events[21]
• SNRIs – venlafaxine	• High doses increase blood pressure	• Not associated with an increased risk of major malformations above the baseline[7] • Exposure linked with transient neonatal discontinuation symptoms[12]	• Moderate exposure, compatible with breastfeeding, careful observation of the infant in higher doses • Minimal adverse events[21]
• Mirtazapine	• May be useful in severe unresponsive hyperemesis gravidarum[24]	• Summary evidence indicates no increased risk of major malformations above the baseline[8]	• Low excretion, compatible with breastfeeding[21]

• Tricyclic antidepressants	• Low risk but serious adverse consequences in overdose[5] • Risk of postural hypotension and anticholinergic side effects	• Not associated with an increased risk of major malformations above baseline[15]	• Most compatible with breastfeeding • Avoid doxepin as two cases of reported significant adverse effects[21]
Antipsychotics – typicals • Chlorpromazine • Haloperidol • Trifluoperazine	• Potential extrapyramidal side effects	• Good safety data showing no increase of malformation[9,15]	• Low excretion compatible with breastfeeding
Antipsychotics – atypicals • Olanzepine • Quetiapine • Risperidone	• Increased risk of gestational diabetes mellitus and weight gain[9]	• Evidence to date seems to indicate no increased risk of congenital malformations, but low numbers[9,25] • Possible increased risk of macrosomia in atypicals[16] • Quetiapine has the least percentage of placental transfer of the atypical antipsychotics[26]	• Low number of studies. Low excretion and probably compatible with breastfeeding[21]
Mood stabilisers • Lithium	• Seek specialist advice early • Check serum levels monthly and thyroid function during pregnancy • Adequate fluid replacement • Special concern around delivery[22]	• Increased risk of overall congenital malformation, as well as specific abnormality, Ebstein anomaly[15] • Avoid particularly first trimester[15]	• High level exposure, controversial use in breastfeeding. If needed under specialist care and monitoring of levels[21,22]
• Carbamazepine	• Need for increased folic acid, 5 mg before conception and in early pregnancy[15]	• Avoid if possible due to increased risk of fetal malformations including neural tube defects[15]	• Limited data suggests safe[22]
• Lamotrigine	• Risk of serious skin rashes including Stevens-Johnson syndrome[5] • Consider 5 mg folic acid supplementation	• Oral cleft 9/1000[15]	• Considered safe for breastfeeding[22]
• Sodium valproate	• Weight gain is common[5] • Need for increased folic acid, 5 mg before conception and in early pregnancy[15]	• Avoid; 17% increased risk of fetal abnormalities, including cardiac and neural tube defects[15] • Concerns for potential adverse effect on neurodevelopment[20]	• Low excretion/compatible with breastfeeding[27]
Benzodiazepines	• Shortest course and lowest dose if indicated[22]	• Rapidly crosses placenta • Some studies show increased risk of oral cleft with first trimester exposure[22] • Avoid during third trimester if possible; floppy baby syndrome in the neonate in high doses[15]	• Low transfer in breast milk but may be dose dependant[22]

- hypotonia and lethargy
- hyperbilirubinemia, and
- large for gestational age infants.[18]

Sodium valproate usage in the first trimester is associated with a rate of up to 20% for serious adverse outcomes, including malformation.[19] Sodium valproate exposure has also been associated with neurodevelopmental abnormalities in the unborn child with continued use throughout the pregnancy.[20] Carbamazepine is also problematic and lamotrigine has been associated with an increased risk of oral clefts in one study.[15]

Benzodiazepines and other drugs

Caution is advised with the use of benzodiazepines in pregnancy (*Table 3*). Principles of use involve using the lowest dose possible for the shortest course. Short to medium acting agents may be more appropriate. Avoid the use of novel hypnotics as there is no safety data available.

Psychotropics and breastfeeding

This issue seems to present a great deal of distress for many women, but there is now good safety data for many medications, including most SSRIs and some antipsychotics and mood stabilisers, with the exception of lithium[21] (*Table 3*).

Principles of care in summary

- Encourage all women with a mental illness and of childbearing age to discuss pregnancy plans.
- Provide and utilise up-to-date information effectively and in a sensitive and individually tailored manner.
- Weigh up risk-benefit analysis on an individual basis.
- Develop a trusting relationship and where appropriate, involve the partner, family members and carers.
- Be sure that adequate systems are in place to ensure continuity of care and effective transfer of information.
- Involvement of specialist care in high risk or complex cases as early as possible.

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