MOOD DISORDERS IN PREGNANCY

Treating psychiatric risk prior to and during pregnancy

Introduction

The point of departure in assessing neonatal risks in women with existing mental health problems is to understand that pregnancy is never risk-free, and that foetal abnormalities, which are random and a risk for all mothers, occur at a rate of 1-3% of live births. The concept of ‘assessment’ is derived from the Latin word ‘assidere’, which means ‘to sit beside’, and this essentially describes the risk evaluation process in consultation with the client.

KEY MESSAGES

- Perinatal psychiatry is benefiting from exciting new research, which provides new approaches to achieving best practice in this field
- Medical practitioners need to take great care not to communicate their perception of the risk of psychiatric medicines to a pregnant patient without being properly informed of the most recent evidence-based risk. To undo an inaccurate message about risk is almost impossible, particularly against the background of media/social media reinforcement of risk
- The risk of relapse with its severe consequences for mother, infant and other family members must be weighed up against the real risk of medication to the unborn infant
- Recent research has shown that the level of neonatal risk of most psychiatric medications is smaller than previously thought or commonly believed.
Risk assessment in women with prior mental illness or women being treated for an existing condition

Mental illness complicates pregnancy and the transition to motherhood while, reciprocally, pregnancy complicates mental illness. In the management of this, clinical algorithms are not useful, as there is a great need for individual assessment. Psychotropic medication complicates pregnancy, but is often essential to avoid serious complications, because pregnancy increases the risk and severity of relapse, for example in insufficiently treated bipolar women. The clinician, whether an obstetrician or psychiatrist, needs to be aware that medicolegal risks are real and keep detailed clinical notes and records. It is important for risk to be assessed on an ongoing basis as pregnancy progresses as well as during the postpartum period; these situations are very dynamic and ever-changing.

The pregnant woman’s risk perception

The first step is to be aware of your client’s perception of their mental illness and preferences regarding the treatment thereof during their pregnancy. Pregnant women, but also their physicians, have an unrealistically high perception of teratogenic drug effects. This leads to an over-estimation of the potential danger of medication. There are numbers of examples that can be drawn from well-conducted studies regarding the risk of persistent pulmonary hypertension of the newborn (PPHN); the difference between the pregnant women from the general population and women on selective serotonin-reuptake inhibitors (SSRIs) is 0.1% vs 0.3%, respectively. It is relevant to remember here that the overall risk of foetal abnormalities in all women is 1-3%.

Equally, the absolute risk of Ebstein’s anomaly following lithium exposure has recently been shown to be 0.1%, following re-evaluation of the earlier data from the 1976 Danish Registry Study. Communication about risk from a healthcare provider has a significant impact on the risk perception of the pregnant woman. “To undo an inaccurate message...”

Figure 1. Risk into context
Prescribing psychiatric medication in pregnancy

At the outset, Dr Vythilingum pointed out that distinguishing whether an abnormality in the newborn is due to the psychiatric condition itself or the effect of medication is complicated, as there are numerous confounding factors. Well-matched control groups are missing from almost all studies and most data are drawn from registry studies where the clinical context in which a particular psychiatric medication is being prescribed is unknown.

Nonetheless, the clinician must draw on available evidence to advise mothers and reduce the risk of a poor neonatal outcome with its consequent effect on the mother, child and other family members.

Use of antidepressants in pregnancy

The use of these medications and their consequences in respect of teratogenicity, PPHN, neonatal adaptation syndrome (NAS), neurodevelopment and post-partum haemorrhage are reviewed here.

Antidepressants and teratogenicity

The major concern addressed is the possibility of cardiac abnormalities, especially with paroxetine (a SSRI).

The conclusions from evidence-based studies show:

1. Antidepressant use has not been found to be associated with congenital heart anomalies in a well-conducted, four-cohort study of different exposure status to SSRIs.

2. A large meta-analysis showed no increase in prevalence of teratogenicity associated with antidepressant use in the first trimester.

3. An evaluation of exposed infants relative to their siblings showed that the higher prevalence of septal defects in the exposed infants disappeared in the sibling comparative analysis, pointing away from a teratogenic effect of these medications.
Mood disorders in pregnancy

The most recent data on SSRIs and non-SSRIs are summarised in Table 2.

### Table 2. Absolute risk of persistent hypertension of the newborn among infants of women with and without antidepressant exposure during pregnancy by class

| Exposure groups | Cohort of women with pregnancies | | | | | |
|-----------------|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                 | Overall | Depression restricted | Overall | Depression restricted | Overall | Depression restricted | Overall | Depression restricted |
|                 | Unexposed | SSR | Non-SSRI | Unexposed | SSR | Non-SSRI | Unexposed | SSR | Non-SSRI |
| Total no. of women | 3 660 380 | 102 179 | 26 771 | 657 515 | 65 316 | 16 283 |
| PPHN no. | 7 630 | 322 | 78 | 1 635 | 221 | 56 |
| Risk per 10 000 (95% CI) | 20.8 (20.4-21.3) | 31.5 (28.3-35.2) | 29.1 (23.3-36.4) | 24.9 (23.7-26.1) | 33.8 (29.7-38.6) | 34.4 (26.5-44.7) |

Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; SSRI, selective serotonin reuptake inhibitor.

It is important to note that the risk of PPHN is raised in caesarean section with an odds ratio of 3.2, while the absolute risk of antidepressant exposure in late pregnancy (90 days before delivery) was small and more modest than suggested earlier.6

### Lithium in pregnancy

In considering this topic, the premise is that the drug you prescribe in pregnancy must have worked in the patient prior to pregnancy, i.e. the lithium treatment must have been successful before. A recent meta-analysis has shown that the absolute risk of Ebstein's anomaly or cardiotoxicity is small (0.05-0.1%)7 and that lithium is considered to be the safest mood stabiliser for bipolar mood disorder type 1 during pregnancy.

In a retrospective study involving more than one million pregnancies in women enrolled in Medicaid and delivered between 2000-2010, the risk of cardiac malformations following lithium treatment in the first trimester was compared to unexposed infants and in a secondary analysis, an evaluation of the mood stabiliser, lamotrigine.8 The results are summarised in Table 3. This has led to a recommended divided-dose strategy9 for lithium in pregnancy (300mg four times a day or 400mg three times a day). This is the safest regimen (compliance must be monitored). Dosage is important, as established in the Medicaid study, and should preferably be under 1g/day.

### Monitoring of lithium levels during pregnancy

It is essential to monitor lithium blood levels until 34 weeks of pregnancy, then weekly until delivery and twice-weekly for the first two weeks postpartum as ‘spiking’ has been seen post-delivery.
Table 3. Lithium in pregnancy

- Cohort study of lithium exposure
- 1,325,563 pregnancies

- Cardiac anomalies
  - infants exposed to lithium 2.41%
  - non-exposed infants 1.15%
  - infants exposed to lamotrigine 1.39%
  - adjusted risk ratio 1.65
    » 1.11 (95% CI: 0.46-2.64) for a daily dose of 600mg or less
    » 1.60 (95% CI: 0.67-3.80) for 601-900mg
    » 3.22 (95% CI: 1.47-7.02) for more than 900mg

- Specific right ventricular outflow tract obstruction defects (Ebstein-like anomalies)
  - 0.60% among lithium-exposed infants versus 0.18% among unexposed infants (adjusted risk ratio: 2.66; 95% CI: 1.00-7.06)

- Results were similar when lamotrigine-exposed infants were used as the reference group

Other mood stabilisers

Table 4 summarises the findings on use of these medications in the perinatal period.

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<th>Table 4. Other mood stabilisers</th>
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<td>Valproate should never be used</td>
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<td><strong>Carbamazepine (CBZ)</strong></td>
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<td>Two- to 10-fold increased risk of neural tube defects (NTDs) in women with epilepsy taking CBZ; however, the risks associated with CBZ are not as great as those associated with valproic acid</td>
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<td>No risk of ongoing neurodevelopmental delay</td>
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Lamotrigine levels should be monitored every four weeks and the dose increased by 20-25%, if less than baseline due to an increase in oestrogen levels. Post-delivery dosages should be decreased by 25% every 1-2 weeks until pre-pregnancy levels are reached. During breastfeeding, the infant should be monitored. In South African settings this may not be practical, so clinicians should be guided by clinical response.
Atypical antipsychotics (second-generation antipsychotics (SGAs))

Experience with these agents is summarised in Table 5.9

Table 5. Atypical antipsychotics

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<th>Source: Atypical Antipsychotic Registry</th>
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- Absolute risk of major malformations is 1.4% for exposed infants vs 1.1% for unexposed infants = odds ratio: 1.25 (95% CI: 0.13-12.19)
- Meta-analysis of SGAs during the first trimester of pregnancy shows:
  - Significant increased risk for major congenital malformations (odds ratio: 2.03; 95% CI: 1.41-2.93)
  - Absence of a specific pattern of malformations makes it difficult to identify overt risk posed by SGAs
  - Some evidence suggests an association between antipsychotic use in pregnancy and the development of gestational diabetes
  - Possible association between antipsychotic medication use in pregnancy and increased neonatal respiratory distress and withdrawal symptoms

Weight gain as a side-effect of antipsychotics

Weight gain leads to unfavourable obstetric outcomes and long-term maternal complications, also a higher incidence of large-for-gestational age neonates. It is relevant to note that there is less weight gain on risperidone as compared to olanzapine, quetiapine and clozapine. There are very few data on weight gain with aripiprazole, ziprasidone and amisulpiride.

Conclusion

It is important to individualise therapy when considering ongoing medication for the pregnant patient. The risk of relapse with its severe consequences for both mother and infant should be weighed up relative to the risk of taking medication during the pregnancy. It is always important to use previous effective therapies and provide social and therapist support throughout the pregnancy.

References