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Prescribing for psychiatric disorders in pregnancy and lactation

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The most recent Confidential Enquiry into the causes of maternal deaths during the perinatal period in England and Wales (1994–1996) revealed that psychological illness was at least as important as hypertensive disorders. It is therefore important for obstetricians to be aware of a variety of psychiatric conditions as well as the psychotropic medication prescribed and sequelae of continuation or withdrawal of these drugs. Best management, of this particularly vulnerable group of women, requires close liaison with the psychiatric team. This chapter considers four groups of women most likely to be prescribed psychoactive drugs during the perinatal period: (i) women with mental illness wishing to conceive, (ii) women with mental illness who conceive while taking medication, (iii) those who become mentally ill while pregnant, and (iv) those who become unwell postnatally. Guidelines for treatment are discussed.

Key words: perinatal; psychotropics; prescribing; pregnancy; postnatal illness.

Women are at increased risk of psychological illness during pregnancy and the puerperium. The most recent Confidential Enquiry into maternal deaths during the perinatal period in England and Wales (1994–1996) revealed that psychological causes were at least as important as those directly due to hypertensive disorders, with 28 reported during this triennium.[1] Up to half the pregnancies in England and Wales are unplanned, and women suffering from mental illness are at particular risk of unplanned pregnancy. Unfortunately, embryogenesis is most sensitive to disruption early in the first trimester. Four groups of women most likely to be prescribed psychoactive agents during the perinatal period will be considered:

1. women with mental illness wishing to conceive;
2. women with mental illness who conceive while taking medication;
3. those who become mentally ill while pregnant; and
4. those who become unwell postnatally.

Competent clinical decision-making during this period involves balancing the risks of exposing the fetus/neonate to psychotropic drugs, against the risk of withholding

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treatment from an unwell mother. These risks are difficult to quantify, although there are more data on the risk of withholding treatment in mentally ill women. For example, offspring of mentally ill women have lower birth weights, poorer neonatal condition, and more birth complications than do healthy controls.[2] Women with serious mental illness who become pregnant are also more likely to be without the support of a spouse or significant other, to hold a negative attitude towards their pregnancy and to have an unplanned pregnancy,[3,4] all of which will compound the risk of poor outcome.

These factors highlight the need for close liaison between obstetric and psychiatric specialities in this particularly vulnerable group of women and infants. We would further emphasize that the obstetrician must have at least an understanding of the types of psychotropic medication prescribed, and the sequelae of continuation or withdrawal of these drugs. However, the decision-making process regarding pharmacotherapy is often complex and poorly informed. This chapter highlights general guidelines which we hope will facilitate such decision-making.

MOOD DISORDERS

Depression

Pre-conception

Pregnancy should be considered when prescribing an anti-depressant (AD) to any woman of reproductive age. This should involve a discussion about the risks and benefits of continuing medication should she become pregnant during treatment, as well as an assessment of current contraception. Women with a long history of depression who are managed on maintenance AD may wish to consider stopping treatment prior to conception. This should be discussed with the woman's psychiatric team, as the risk of relapse is high.[5]

Women with residual depressive symptoms should be offered a trial of discontinuation of medication, and may benefit from non-medical interventions such as psychological support or cognitive behavioural therapy (depending on local resources). These alternatives should also be considered in women who are keen to remain on treatment where the clinical indication is not strong. In both cases prophylaxis against a postpartum relapse may be achieved through the re-introduction of AD medication late in the third trimester or early puerperium.[6] Women who are at high risk of relapse and who wish to conceive may have the dose of medication reduced with regular monitoring of symptoms and/or may switch to a 'safer' AD (cf. Table 1). Although no data exist to support the idea, there is a theoretical argument for checking AD plasma concentrations pre-conception in treated women. This pre-conception level *may* help clinicians to use the lowest effective dose and minimize fetal exposure, while maximizing drug efficacy. This is especially important during the perinatal period because AD drug levels decline steadily with gestation and may fall below the therapeutic level.

Antenatal

First trimester. Women at high risk of depressive illness may benefit from education, counselling and enhanced social support prior to childbirth[7] and these options should be considered from the first trimester onwards. Ideally, depressive symptoms in at-risk women should be monitored regularly. The use of recognized rating scales has the advantage of being quick, easily applied by non-psychiatric staff and can form an

Table I. Antidepressant choice in pregnancy and lactation.

CLASS	Drugs	Antenatal exposure	Postnatal exposure/breast-feeding
TCAs (1st line)	Amitriptyline	Most data + no evidence of fetal anomaly	Probably safe
	Imiprimine	Probably safe	Probably safe
	Nortriptyline + Desipramine	Probably safe (preferred by some as less anticholinergic SEs)	Probably safe
(3rd line)	Doxepin	Limited data	Avoid?
	Clomipramine	Limited data	Limited data
	Dothiepin	Limited data	Limited data
	Lofepramine	Limited data	Limited data
Drugs related to TCAs (3rd line)	Mianserin	Limited data	Limited data
	Maprotiline		
	Trazadone		
SSRIs (2nd line)	Fluoxetine	Most data of any SSRI + no evidence of fetal anomaly	Probably safe
(2nd/3rd line)	Sertraline + Paroxetine	Data encouraging but limited	Probably safe (preferred by some as less secretion in breast milk than fluoxetine)
Drugs related to SSRI (3rd line)	Nefazadone		
	Venlafaxine	Limited data (avoid if possible)	Limited data (avoid if possible)
	Mirtazapine		
	Reboxetine		
MAOIs (3rd line)	Phenelzine	Limited data Anaesthetic risks	
			Limited data (avoid if possible)
	Moclobemide	Avoid if possible	

TCA = tricyclic antidepressants; SSRIs = selective serotonin re-uptake inhibitors; MAOIs = monoamine oxidase inhibitors; SE = side-effect.

objective assessment of symptoms when a woman is seen by a number of doctors and different health care workers.

Depression that develops during the first trimester may be difficult to diagnose as depressive symptoms often 'overlap' with those of pregnancy (e.g. loss of energy, fatigue and sleep disturbance). If treatment is required, non-pharmacological interventions, such as psychotherapy,[7] should always be considered before medication and this approach may be especially beneficial in patients with mild to moderate depression. However, moderate to severe depression should always be treated with ADs alongside other treatments. In addition, treatment with electroconvulsive therapy (ECT) should be considered in cases of severe depression. This approach has been found to be both effective and safe in pregnancy.[8] A woman who is treated with an AD during gestation is likely to continue treatment into the postnatal period, so the choice of drug should take into account antenatal exposure and exposure during breast-feeding (see Table 1).

Second trimester. The clinically important feature of this trimester is that organogenesis is almost complete. The dosing requirements of antidepressants increase to an average of 1.6 times the pre-pregnancy dose (range 1.3–2.0) during this trimester.[9] Therefore some clinicians routinely increase the dose of AD. If a plasma level has been measured pre-conception, or early in the first trimester, it can be used to titrate the dose in the latter half of pregnancy as discussed above.

Third trimester. A post-partum 'withdrawal syndrome' involving neonatal irritability, restlessness, hypothermia and convulsions has been described following chronic use of ADs near term.[10,11] Consequently, some authors have suggested stopping ADs 3–4 weeks before the estimated date of delivery.[12] However, the description of this syndrome is based on anecdotal reports, and maternal AD usage may be coincidental. Also, discontinuation of medication at this time is at the point when the risk of depressive illness is at its highest. Monitoring maternal AD drug concentration, especially close to term, and careful observation of the neonate for signs of toxicity, are suggested alternative strategies.[13]

Postnatal

There is a significantly increased risk of depression in the first 5 weeks post-partum.[14] The risk of a post-partum relapse in women with a past history of depression is estimated to be 30%[15] and as high as 50–60% in women with a past history of *postnatal* depression.[16]

Women who have been treated with antidepressants antenatally may have required an increased dose of medication to compensate for the pharmacodynamic changes of pregnancy. These changes return to the non-gravid state approximately 48 hours post-partum. To minimize neonatal exposure to ADs in breast milk the dose of AD should be reduced, if possible, postnatally and titrated against symptoms.

Patients who have a history of severe or recurrent postnatal depression or previous severe depression outside the perinatal period should be considered for pharmacological prophylaxis immediately post-partum.[17] Women with other risk factors should be encouraged to develop formal and informal support networks through friends and family and may also be considered for non-pharmacological interventions (as outlined above), if these are not already in place. The use of non-medical local support networks (e.g. NEWPIN, SURESTART and HOMESTART) is especially valuable at this time.

Research into the effect of non-pharmacological management of postnatal depression is limited. However, a recent randomized controlled trial found that 12 sessions of cognitive behavioural therapy administered by trained health visitors was as effective as fluoxetine in the treatment of mild to moderate postnatal depression.[18]

Tricyclic antidepressants (TCAs) and related drugs

Exposure during pregnancy

TCAs such as amitriptyline and its derivatives have been used widely to treat depression since the 1960s. Consequently, there is more information regarding their use in the perinatal period than for other antidepressant medication. In a meta-analysis of 14 studies, over 300 000 births have been assessed following exposure to TCA medication during pregnancy, including over 400 cases of first-trimester exposure.[19] There is no evidence that they are associated with an increased risk of congenital malformations, miscarriage, pre-term delivery or growth restriction.[13] Furthermore, comparison of 80 children postnatally has failed to reveal any evidence of a reduction in IQ scores, language development or of behavioural problems.[20] However, data are limited for the safety of newer TCAs such as clomipramine, dothiepin, doxepine and lofepramine. Although there is no suggestion that they are associated with a higher risk of complications, they are not recommended as first-line treatment in the perinatal period. Other TCAs that may be preferable include nortriptyline and desipramine because they have less anticholinergic side-effects and are therefore less likely to exacerbate postural hypertension.

Breast-feeding

TCAs are also the most widely studied ADs in breast-feeding. Studies suggest that all TCAs may be detected in breast milk at concentrations similar to that in maternal plasma.[21] In addition, there have been three reports of TCA detection in infant plasma.[22] One of these case reports described detectable plasma levels of an active metabolite of doxepin (N-desmethyldoxepin (DDP)) in an infant of a mother who was being treated with doxepin. The infant concerned was additionally noted to be pale, limp and drowsy with shallow respiration which improved 24 hours after cessation of breast-feeding.[23] It is therefore advised to avoid breast-feeding if the mother is taking this TCA. Some authors have extended this caution to other TCAs. The discrepancy in clinical practice is highlighted by the most comprehensive meta-analysis of the literature, which consists of only 66 mother–infant pairs.[21] If a women requires AD de novo postnatally, then the safest practice is to prescribe one with a short half-life. To avoid peak plasma levels, mothers should receive once-daily dosing in the evening, feed with formula overnight and recommence breast-feeding during the day.

Related antidepressants

There are no published data for maprotiline, mianserin or trazodone in either pregnancy or breast-feeding. Case reports from both the manufacturers and the National Teratology Information Service do not suggest an increased risk of congenital abnormalities or postnatal complications, but these drugs should be avoided if possible.

Selective serotonin re-uptake inhibitors (SSRIs)

Exposure during pregnancy

Although there is no conclusive evidence of increased efficacy of selective serotonin re-uptake inhibitors (SSRIs) over other antidepressants, fluoxetine (Prozac) is currently the most widely prescribed AD worldwide. The manufacturer's data sheet contains nearly 2000 cases in pregnancy with no evidence of an increase in congenital abnormalities or a clustering of any particular type of malformation.[24] Furthermore, a study of neurobehavioural function in children up to 4 years of age who had been exposed to fluoxetine in utero, has failed to detect any difference compared to a non-exposed control group.[20]

Data on neonatal outcome following in utero exposure to other SSRIs are limited. Consequently their use cannot be recommended in pregnancy. However, in the clinic some patients respond better to some SSRIs than to others. Close multiprofessional liaison will determine whether change to a 'safer' AD is indicated.

Breast-feeding

There are few data on the safety of SSRIs in breast-feeding. There is a single case report of gastrointestinal symptoms in a 6-week-old infant following breast-feeding from a mother treated with fluoxetine that resolved when the infant was switched to bottle-feeding.[25] A recent prospective study followed up four infants for 13 months following exposure to fluoxetine during breast-feeding and failed to detect any evidence of developmental abnormality.[26] Follow-up of a child until 21 months after breast-feeding from a mother treated with fluvoxamine 200 mg/day also failed to suggest any developmental abnormality. Sertraline (Lustral®) and paroxetine (Seroxat®) have been found to be secreted in breast milk at lower concentrations than fluoxetine,[10] and sertraline, with its relatively short half-life, is commonly used as a once-daily evening dosing regime as described earlier.

Drugs related to SSRIs

Information on other antidepressants, including venlafaxine, nefazadone, mirtazapine and reboxetine, is limited to a handful of case reports. Although there is no suggestion of an increased risk of congenital or neurodevelopmental anomalies it is advisable to avoid these medications in the perinatal period if possible.

Monoamine oxidase inhibitors (MAOIs)

There is limited evidence for detrimental effects of monoamine oxidase inhibitors (MAOIs) in pregnancy, but they may interact with analgesic and anaesthetic drugs as well as tyramine-rich food and are therefore best avoided.[27]

Moclobemide is a reversible MAOI that binds specifically to the type A receptors (RIMA). It is claimed to cause less potentiation of the pressor effect of tyramine than the traditional irreversible MAOIs, but no published data exist on its use in human pregnancy and it is therefore not recommended.

Bipolar affective disorder (BPAD)

BPAD affects 1–2% of the population.[28] Drugs used to treat BPAD include lithium, carbamazepine, sodium valproate and newer antiepileptic drugs such as lamotrigine and gabapentin.

Pre-conception

As with all psychotropics, contraception must be discussed at the time of prescribing mood stabilizers. Additionally, clinicians must be aware that some drugs (e.g. carbamazepine) induce liver enzymes and reduce the efficacy of oral and depot contraceptives.

Discontinuation of mood stabilizers in non-gravid women with BPAD is associated with a significant risk of relapse, and this risk is greater following rapid discontinuation of medication.[29] Recent research suggests that these risks remain in pregnancy.[30] The main advantage of planning conception in this group is that if medication *is* to be withdrawn, it enables it to be done gradually with close monitoring, which limits the chance of a relapse. It has been argued that one should wait until early pregnancy before stopping medication in order to provide prophylaxis for the longest period while at the same time minimizing fetal exposure.[31] Any decision to stop treatment should be made with the multiprofessional team and the patient.

If a woman chooses to stop medication she should be aware that the risks of relapse include more than simply the need to re-commence medication. Relapse is determined clinically, and this means that she is likely to become unwell before treatment can be restarted. During this period she may put herself and, if already pregnant, her fetus, at risk. She would also then be at risk of receiving higher doses of medication and multiple drugs. When medication is withdrawn pre-conception, the option of recommencing medication towards terms or in the first 48 hours post-partum should also be discussed (see below).

For women who continue with maintenance medication, monotherapy is recommended and plasma levels should be kept at the lower limit of the therapeutic range in an attempt to reduce the risk of teratogenesis. Similarly, to reduce the plasma peaks of medication, patients should be switched to slow-release compounds or have doses divided. There is evidence to suggest that folic acid (0.4 mg/day) may prevent neural tube defects in all women if given during the early stages of embryogenesis.[32] Both carbamazepine and sodium valproate are folic acid antagonists, so a higher dose (5 mg/day) of folic acid is recommended pre-conception. See also anticonvulsants in Chapter 4.

Antenatal

First trimester. The main dilemma for women who present to their physician on maintenance therapy during this trimester is whether or not to continue with their treatment. As stated above, there is an increased risk of relapse if medication is stopped abruptly. However, a slower reducing regime of medication may result in the drug being administered through even more of the first trimester. Research is still required to determine the optimum time over which mood stabilizers should be stopped in pregnancy.

Management of women who remain on maintenance therapy is also complex. Mood stabilizers, unlike other psychotropic agents, function within narrowly defined therapeutic ranges. Consequently, drug levels should be monitored throughout pregnancy to

ensure that levels remain within these ranges. For lithium, levels should be taken monthly, along with urea and electrolyte (U/Es) and thyroid functions tests (TFTs). Protocols for the measurement of anticonvulsants are less clear, but plasma levels should probably be checked equally frequently and the dose of medication adjusted accordingly.

It is uncommon for women to have either a relapse or first episode of mania during pregnancy,[33] but if this occurs, she will usually require hospital admission. In addition to a mood stabilizer, rapid symptom relief is obtained with sedative antipsychotic medication such as chlorpromazine or haloperidol. ECT therapy may also be necessary.

Women with a past history of bipolar affective disorder, who are not receiving maintenance treatment, are at high risk of a post-partum psychosis (with an estimated risk of 30–50%[31]) and should be reviewed by a psychiatrist during the first trimester.

Second trimester. Women on lithium treatment require plasma lithium levels (as well as U/Es and TFTs) to be checked fortnightly in the second trimester due to the rapid changes in drug metabolism and distribution. The dose of lithium usually needs to be increased as the pregnancy progresses. It is less clear how frequently anticonvulsant levels should be checked, but monthly levels are generally considered adequate. All women on a mood stabilizer require a detailed ultrasound scan during the second trimester to screen for anomalies, such as neural tube or cardiac defects; those receiving lithium should also be considered for a fetal echocardiogram. See also Chapter II (drugs to avoid in pregnancy). Manic episodes during this time should be managed as in the first trimester.

Third trimester. Weekly lithium levels are required in the third trimester to monitor the fall in plasma levels and/or alterations in renal or thyroid function. Preparations for delivery may also be made towards the end of this trimester. Given the high rate of relapse in this group, some advocate a planned delivery via Caesarean section. This approach allows careful management of mental state and lithium levels between the obstetric and psychiatric teams. Alternatively, if vaginal delivery is planned, it is generally advised that lithium plasma concentration be reduced prior to delivery, due to the volume changes and possible dehydration that may occur at delivery. Some advocate reducing the lithium dose by 25–30% on the day before the estimated date of delivery (EDD). Because the majority of women do not deliver on their EDD, a more practical solution is to reduce the dose by 50% (or to the pre-pregnancy dose) at the onset of labour.[34]

Despite these measures, there have been reports of neonatal toxicity in babies exposed to lithium at the time of delivery.[35] Thus, some suggest withdrawal of medication in the month prior to delivery or towards the end of the third trimester, depending on individual needs. These toxic effects are, however, both rare and apparently self-limiting. They are usually absent by 14 days, corresponding with the delayed renal elimination of the drug in the neonate.

Even when maintenance medication has been successfully stopped antenatally, the greatest risk of relapse remains the post-partum period. Prophylaxis may be achieved by administering medication close to term. Evidence supporting this approach is limited to a few studies involving lithium administration.[36] Data for the prophylactic potential of other mood stabilizers are lacking and further research is urgently required in this area.

Postnatal

To prevent maternal toxicity in the immediate post-partum period, fluid balance must be maintained and plasma levels of mood stabilizers checked. Although neonatal toxicity is rare it is also important to observe the neonate for any symptoms.

Women who develop a manic episode post-partum are best managed in hospital, possibly in a dedicated mother-and-baby unit. Pharmacological management is similar to that in the antenatal period and involves treatment with mood stabilizers, as well as an antipsychotic in the manic phase. With the exception of ECT, the role of non-pharmacological treatment in women who relapse in the post-partum period has not been assessed.

In women at high risk of relapse of BPAD there is some evidence that administration of prophylactic lithium may be beneficial if given within 48 hours of delivery.[37]

Lithium

Exposure during pregnancy

It has been estimated that 1 in 2000 people in the UK are prescribed lithium.[38]

A pooled review of two cohort and four case-controlled studies has estimated the risk of Ebstein's anomaly following first-trimester exposure to lithium to be approximately 1 in 1000–2000.[39] Thus, although the *relative* risk is 10–20 times greater than the 1 in 20 000 risk found in the general population, the *absolute* risk remains small. A 5-year follow-up of 60 children exposed to lithium in the second and third trimesters did not reveal any developmental anomalies compared to their siblings.[40]

Breast-feeding

Two case reports detail detrimental effects of breast-feeding in the neonate attributable to lithium exposure.[41,42] In the latter, the infant was breast-fed without problems for over 2 months. 'Signs of toxicity' occurred only during a respiratory tract infection and recovery followed discontinuation of breast-feeding; it is likely that intercurrent illness and dehydration precipitated the toxicity. Although current data do not support the view that lithium is toxic during breast-feeding, most clinicians do not recommend breast-feeding while taking lithium owing to the theoretical risk of infant toxicity. However, in women who do breast-feed, close monitoring of the infant is required and it is advisable to avoid breast-feeding during neonatal or infant illness. If signs of toxicity occur, breast-feeding should be suspended until infant and maternal levels of plasma have been obtained. As with ADs, mixed feeding is probably preferable.

Anticonvulsants

Exposure during pregnancy

The teratogenic potential of carbamazepine and sodium valproate is discussed in Chapter 4.

Table 2. Mood stabilizer choice in pregnancy and lactation.

Class	Drug	Antenatal exposure	Postnatal exposure/breast-feeding
Lithium salts	Lithium carbonate (1st line)	Ebstein's anomaly (1 in 1 000–2 000 in first trimester)	Controversial (avoid during intercurrent neonatal/infant illness)
Anticonvulsant	Carbamazepine (2nd line)	Increased NTD (? 0.5–1%)	Probably safe
	Sodium valproate (3rd line)	Increased NTD (1–2%)	Probably safe
	Lamotrigine (4th line)	Limited data	Limited data
	Gabapentin (4th line)	Limited data	Limited data

NTD = neural tube defect.

Anxiety disorders

Pregnancy is associated with a significant increase in general symptoms of anxiety in all women and has a variable effect on the anxiety disorders ranging from resolution to worsening of symptoms.[43] Post-partum, anxiety disorders worsen[44] although breast-feeding has an anxiolytic effect.[45]

Pre-conception

Women taking anxiolytic medication who wish to conceive should consider reduction and cessation of drug therapy. Liaison with psychiatric colleagues is important as these patients often have chronic, hard-to-treat symptoms that may interfere with obstetric management. Reduction of anxiolytics should be combined with alternative non-pharmacological interventions such as supportive and cognitive behavioural therapy.

Antenatal

Anxiolytics should be avoided during this period. If considered essential, prescription should be on a short-term basis at the minimum effective dose. Women on maintenance therapy should be managed as described above. In women who develop anxiety disorder during the first trimester, most can be managed non-pharmacologically with education, supportive care, and re-assurance. Pharmacological therapy should be reserved for the most severe cases.

Postnatal

Mothers should be observed for deterioration in symptoms. Observation of the neonate during this period is equally important as fetal exposure to benzodiazepines (BZs) in the third trimester, or during parturition, is associated with a neonatal withdrawal syndrome (diazepam doses $>$ 30–40 mg/day or chronic exposure increases the risk of neonatal withdrawal).[46]

Benzodiazepines (BZs)

Exposure during pregnancy

Up to 30–40% of pregnant woman may be prescribed BZs.[31] Early reports of a tenfold increase of cleft palate following first-trimester exposure to BZs (0.06 to 0.7%)[47] are not supported by the largest and most recent meta-analysis. Following a review of over 1400 studies, no significant relationship was found between fetal exposure to BZ and oral cleft.[48] However, limited human data exist for newer BZs, such as clonazepam.

Breast-feeding

Diazepam can accumulate in breast milk and in breast-fed infants; single doses are probably harmless. Shorter-acting compounds such as temazepam may be preferable, if absolutely necessary.

Antihistamines

Exposure during pregnancy

The antihistamine promethazine is a simple hypnotic with anxiolytic properties. With the exception of brompheniramine, antihistamines have not been found to be associated with an increased risk of congenital anomalies. These agents could be considered as simple hypnotics in pregnant women.[49]

Other hypnotics

Exposure during pregnancy

The newer, non-BZ agents, such as zopiclone and zolpidem, have a similar potential for dependency as the BZs. Although neither has been found to be teratogenic in animals, human studies are limited. Occasional use is considered safe, but otherwise guidelines for BZs should be followed.

Breast-feeding

Zopiclone is excreted in appreciable amounts in breast milk and is contraindicated unless only an occasional dose is required. No data are available for zolpidem.

SCHIZOPHRENIA SPECTRUM DISORDERS

Early literature reported that women with schizophrenia had reduced fertility, but conception rates may be increasing due to a combination of de-institutionalization and antipsychotic agents that cause less disruption of the hypothalamic gonadal axis. About half of the women who suffer with schizophrenia become mothers. For some, pregnancy is a time of increased well-being and an opportunity to be accepted in society; but in general, schizophrenic symptoms do not improve and may worsen during pregnancy.[50,51]

Only about half the women with schizophrenia who become mothers continue caring for their infants.[52] While, for some, motherhood has a very positive impact on their health, and results in reduced social stigma and a more meaningful work role

with improved social networks,[53] the extra stressors involved in child-rearing become particularly potent in this vulnerable population. The need to optimize mental health in a pregnant or post-partum woman with schizophrenia is clear. All mothers need extra support; those with chronic and severe mental illness have a particular need, yet it is this group who are often the most materially and socially deprived.

Schizophrenia differs from chronic depression in a number of important ways. Subtle cognitive deficits may affect a woman's capacity to monitor herself in pregnancy and to comply with antenatal care; these same deficits, and those associated with disturbances of affect, may impinge on her capacity to respond to an infant's needs. Psychotic symptoms may also cause more functional impairment than depressive symptoms.

For these reasons, women with schizophrenia are likely to be treated with an antipsychotic agent throughout gestation. However, few data exist to guide clinicians about which drug or which dose to use. The following is a guide, but each patient should be assessed individually by their multiprofessional team with involvement of significant others as appropriate.

Pre-conception

Women with schizophrenia are less likely than healthy women to plan their pregnancy[54] and are more likely to have an unwanted pregnancy, to become pregnant through rape and to harbour negative feelings about their pregnancy.[55] Women with schizophrenia may also be more likely than healthy women to have an adverse pregnancy outcome.[56] It is vital that professionals in contact with this group are constantly aware of their contraceptive needs and provide education regarding the risks of conception while unwell or medicated.

Women with schizophrenia who do plan their pregnancy should be given advice about nutrition, substance misuse and general self-care, and should receive an increased dose of folic acid if treated with a mood stabilizer in addition to an antipsychotic drug (APD). Medication should be reviewed, and those well enough may have their maintenance dose reduced to a safe minimum or gradually withdrawn. Most women with schizophrenia, however, are maintained on treatment. Unless there are particular contraindications, atypical antipsychotics should be switched to either *low potency* chlorpromazine (with which there is most experience) or to a *high potency* agent, such as trifluoperazine or haloperidol, prescribed at the minimum effective dose.

Antenatal

First trimester. Most women with schizophrenia will not present to a clinican until 6–8 weeks' gestation, when organogenesis is almost complete. However, as 'behavioural teratogenicity'[57] may occur on a different time scale, review of medication after this time is equally important.

Increasing numbers of women with schizophrenia are prescribed atypical antipsychotics. Most data are available for clozapine and olanzapine, but it is still our recommendation that women be changed to a high potency, classical compound such as trifluoperazine or haloperidol, as described above. However, these agents carry an increased risk of extrapyramidal movement disorder (which is dose-related) and there *is* a risk of relapse when switching drug.

If a woman becomes floridly psychotic during pregnancy, hospital admission (preferably to a specialist mother-and-baby facility) is necessary. In those presenting with a first episode of psychosis, alternative diagnoses must be considered (e.g.

cerebral event; drug or alcohol-induced psychosis) and initial assessment should be free of medication within a safe hospital setting.

Second trimester. As pregnancy progresses, the physiological changes of pregnancy may reduce the efficacy of APDs. Close monitoring of women by the multiprofessional team is vital so that drug dose can be titrated against symptoms. As with other psychotropic agents, women receiving treatment should be offered a detailed ultrasound screening for congenital anomalies.

Third trimester. If a woman has required APD treatment throughout pregnancy it is unlikely that she should have her medication withdrawn at this time, despite the risk of neonatal withdrawal symptoms. Best practice involves multiprofessional assessment of individual cases. If local resources include a 'mother-and-baby' unit, women should be encouraged to visit it towards term.

Postnatal. Prophylactic admission to a specialist mother and baby unit should be considered in the early postnatal period. The neonate should be monitored for signs of toxicity.

Breast-feeding

As with other psychotropic agents, antispychotics all attain measurable levels in breast milk and infant plasma, although these are generally very low, especially with typical antipsychotics.[21] Levels of these drugs should decrease as hepatic metabolic mechanisms mature in the infant, but we would advise mixed or supplemented feeding of infants using formula milk with avoidance of feeding at peak levels.

Typical antipsychotics

Chlorpromazine (CPZ) (low potency)

In a study of 52 children followed until 2–4 years of age, *low-dose* CPZ (up to 200 mg/day) was not associated with morphological or developmental anomalies.[58] The largest study of 142 mothers treated in the first trimester showed no abnormal outcome at 4 years.[59] However, a study of three women who received *high-dose* CPZ (500–600 mg/day) reported neonates who suffered with respiratory distress and cyanosis[60]; extrapyramidal side-effects have also been reported in neonates. Some clinicians therefore advocate reduction in doses pre-term while others recommend switching to high-potency agents which have fewer autonomic side-effects.[61]

Trifluoperazine (TFP) (high potency)

In 480 pregnant women treated with TFP there was no increased incidence of abnormalities.[62] Forty-two women with first-trimester exposure showed no reduced IQ or developmental problems in children at 4 years.[59]

Haloperidol (high potency)

Two large studies have not found an excess of birth defects in infants exposed to low-dose haloperidol in the first trimester.[63] In some women it may preferred to CPZ,

although it should be avoided pre-conception because of hyperprolactinaema, which may disrupt the ovarian cycle. In addition, some clinicians recommend avoiding the drug antenatally because of anticholinergic side-effects which may exacerbate postural hypertension.

Flupenthixol and fluphenazine (high potency)

Limited data do not suggest an increased incidence of fetal or neonatal abnormalities associated with these agents. In general, depot preparations should be avoided as they often produce greater variation in drug blood levels. However, some women fail to comply with oral preparations, making depot necessary.

Breast-feeding. A recent study[64] examined 12 mothers who breast-fed their infants while taking haloperidol, chlorpromazine or trifluoperazine. Repeated clinical and developmental assessments of the breast-fed infants were carried out up to 30 months of age. Concentrations of haloperidol in the adult range were found in plasma from two of five infants, but there was no evidence of any acute or delayed adverse effects. Three other breast-fed infants whose mothers were prescribed both haloperidol and chlorpromazine showed a decline in their developmental scores from the first to the second assessment at 12–18 months. No conclusions can be drawn from such limited data; if women are keen to breast-feed we would advise mixed feeding as described.

Atypical antipsychotics

Olanzapine

A prospective follow-up to 20 mothers exposed to varying doses of olanzapine during first and/or second and/or third trimesters has failed to find an increased incidence of major malformations or birth complications.[65]

Risperidone

There is a lack of human data. It is advised to avoid this drug unless there is a particular indication.

Amisulpiride

As above.

Quetiapine

As above.

Clozapine

Women may be more likely to conceive on clozapine than on other typical APDs as (i) it does not increase prolactin levels and (ii) may improve the social functioning in women with schizophrenia. To date, the evidence does not suggest adverse fetal outcome in women exposed to relatively low doses of clozapine in pregnancy.[66]

Breast-feeding. No data are available for the atypical APDs during breast-feeding, and it is advised that women avoid feeding if taking these drugs.

SUMMARY

The management of psychiatric illness and prescribing in the perinatal period is summarized below.

Pre-conception

- Consider delaying conception until illness in remission
- Discuss and document contraception
- Discuss teratogenic risk of medication
- Discuss continuation/withdrawal or reducing dose of medication in women currently receiving treatment
- Discuss/offer non-pharmacological treatment where appropriate
- Consider switching to a 'safer' medication
- Liase closely with psychiatric team

First trimester

- Discuss teratogenic risk of medication
- Discuss continuation/withdrawal or reducing dose of medication in women currently receiving treatment
- Discuss/offer non-pharmacological treatment where appropriate
- Consider switching to a 'safer' medication
- Monitor symptoms of illness (e.g. using recognized rating scales)
- Liase closely with psychiatric team

Second trimester

- Check plasma level of medication and/or consider increasing dose of medication to compensate for physiological changes of pregnancy
- Offer screening for fetal anomalies (e.g. detailed ultrasound, echocardiogram)
- Monitor symptoms of illness (e.g. using recognized rating scales)
- Liase closely with psychiatric team

Third trimester

- Discuss mode of delivery
- Inform anaesthetist of medication
- Consider prophylactic medication in women at high risk
- Consider visiting mother-and-baby unit if high risk of requiring admission
- Consider reducing dose of medication
- Liase closely with psychiatric team

Post-partum

- Inform paediatricians of maternal medication/monitor for signs of toxicity

- Encourage mixed feeding
- Liase closely with psychiatric team
- If mentally unwell post-partum admit to dedicated 'mother-and-baby' unit (if possible)

Education

- Impact of mental health and illness on pregnancy and fetus/neonate
- Impact of pregnancy on mental health in at risk or ill women
- Impact of treatment on fetus/neonate; implications for breast-feeding
- Importance of planning and good antenatal care
- Implication of mental health to mother's capacity to care for newborn

Counsel

- Allow woman to vent feelings
- Be non-judgemental in response
- Help in problem-solving
- Encourage woman to draw on her own psychological resources
- Informally review mental state

Support

- Encourage to plan antenatal and postnatal period
- Provide a forum for partner to be involved where appropriate
- Facilitate family and informal support networks
- Practical solutions to practical problems
- Advise re local facilities, for example NEWPIN, SURESTART

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