Psychotropic medication in pregnancy

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Abstract The risks and benefits of psychopharmacological treatment in pregnancy need careful consideration. Conventional antipsychotics and tricyclic antidepressants are relatively safe for the foetus. Selective serotonin reuptake inhibitors appear to be safe, but mood stabilisers such as lithium, sodium valproate and carbamazepine are associated with increased foetal malformations. Benzodiazepines in the first trimester are teratogenic, and in high dosage can also cause withdrawal symptoms, hypotonia and agitation in the newborn. Women taking atypical antipsychotics should be switched to conventional antipsychotics before they conceive. In women with long-term mental illness necessitating psychotropic medication, effort should be made to stop polypharmacy and non-essential medication (e.g. benzodiazepines) and to decrease the dose of essential drugs, after full assessment. There is rarely a valid reason to stop essential drug treatment during pregnancy.

The management of psychiatric problems and pharmacological treatment in pregnancy is complex, difficult and burdened with many biological and personal factors. Psychiatrists need to consider the impact of untreated illness on the mother and the foetus as well as the possibility of increased risk of obstetric complications and congenital malformations associated with pharmacological treatment.

Studies show that pregnancy can be a difficult period, during which psychosocial, lifestyle and also hormonal changes lead to an increased incidence of mental health problems such as depression, anxiety disorders, obsessive and compulsive disorders, episodes of personal and psychosocial crises, exacerbation of existing severe mental health problems and recurrence and relapse of previously successfully treated disorders (Kendell *et al*, 1987; Sickel *et al*, 1993).

Hormonal changes during this period, emotional stress, and personal and social changes in the life of the expectant mother all affect the course of the mental health problems. Some such problems come to attention for the first time during pregnancy, as a result of the increased professional contact. However, other conditions may be masked by the pregnancy and therefore not receive the attention they deserve. The Confidential Enquiries into Maternal Deaths in the UK (Oates, 2001) have shown the period of pregnancy to be loaded with psychological problems and an increased risk of suicide, all in need of better recognition by psychiatrists as well as by non-psychiatric professionals.

Risk–benefit assessment

Risk–benefit assessment involves assessing the potential effect of illness on the mother, the foetus and the family, and the potential effects of treatment on the mother and the foetus. The ultimate goal of risk–benefit assessment is to limit exposure to the illness and/or treatment. It aims to help the patient and those caring for her to decide which treatment poses the least risk.

To date, the effects of untreated psychiatric illness on the developing foetus have limited reliable documentation. However, the impact on the foetus of the unhealthy lifestyle of women with untreated illness, involving such factors as poor diet, the possibility of increased smoking, drinking and drug misuse, lack of exercise, impaired self-care, unhygienic living conditions and poor compliance with prenatal appointments is well documented. Suicide during the perinatal period is a serious risk in women with mental health problems (Oates, 2001).

Antenatal depression and anxiety have been linked to low birth weight and smaller head circumference (Orr & Miller, 1995; Zuckerman *et al*, 1990). Depression has an impact on obstetric outcome; it increases the risk of low birth weight and preterm births (Orr & Miller, 1995). Untreated mental illness that continues into the postnatal period affects the well-being of the infant: depression leads to impaired attachment, impaired cognition and increased behavioural disturbances, and its effects in later life are complex and multi-factorial. There is limited information about the effects on the child of

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mania, psychosis and minor but persistent psychiatric morbidity (Murray & Cooper, 1977; Rutter, 1997).

In the treatment of pregnant women, the current consensus is that no decision is risk-free but that mental health complications outweigh the risk of pharmacotherapy. There is no barrier between maternal blood and the placenta, therefore psychotropic medication used in pregnancy reaches the foetus; nevertheless, placental transfer of psychotropic medication – especially antidepressants – is highly variable. To date, we have no evidence of excessive placental passage of either antidepressant or psychotropic drugs, but increased maternal dosage typically increases umbilical cord passage, resulting in higher serum levels in the infant.

Although evidence about treatment during pregnancy is limited and we are unable to answer many questions arising from it, a useful treatment should not be stopped without a clear and plausible reason. Neonatal toxicity, prematurity and stillbirth, and morphological and behavioural teratology are potential risks and need to be considered (Koren *et al*, 1998). Reports of side-effects of psychotropic medication, risks to the foetus and infant, and malformations associated with non-psychotropic and psychotropic medication have been published (Butters & Howie, 1990; Briggs *et al*, 1994; Rubin, 1995).

It is important to note that while evaluating the safety of drugs, not only anatomical malformations but also long-term behavioural teratogenicity should be explored. There is limited information about behavioural problems caused by psychotropic medication intake during pregnancy, but it is clear that untreated mothers may fail their children to the point of neglect and maternal separation, with its potential adverse effects in adulthood.

Consideration needs to be given to the difficulties in differentiating between environmental, social or personal factors and any pharmacological effects of medication in pregnancy that lead to behavioural problems.

Risk–benefit discussion should involve the patient and her carers, all of whom should be very clear about both the side-effects of treatment and the problems associated with lack of treatment. The possibility of alternative treatment methods and their strengths and weaknesses should be discussed.

Pharmacokinetics and pharmacodynamics

There are significant differences between men and women in the pharmacokinetics and pharmacodynamics of psychotropic medication (Hamilton &

Yonkers, 1996). Furthermore, pregnancy causes major pharmacokinetic and pharmacodynamic changes in the body (Little, 1999): these include delayed gastric emptying, decreased gastrointestinal motility, increased volume of distribution, decreased drug binding capacity, decreased albumin levels and enhanced hepatic metabolism with induced liver metabolic pathways (Stowe & Nemeroff, 1998). There is also greater renal clearance and the glomerular filtration rate increases. Plasma volume increases by 5%. The foetus has lower plasma protein binding, lower hepatic functioning, relatively increased cardiac output and greater permeability in the blood–brain barrier in comparison with adults (Stowe & Nemeroff, 1998). These changes all point to the importance during pregnancy of cautious prescribing, the need for lower doses of medication and monotherapy, and regular follow-up for any possible side-effects, in order to protect both mother and foetus.

Psychotropic medication

Psychotropic medication includes antidepressants, mood stabilisers such as lithium, anti-epileptics such as carbamazepine and sodium valproate, conventional and atypical antipsychotics, benzo-diazepines and anticholinergics. Drugs of misuse and alcohol are known to have detrimental effects on the foetus. Comorbidity in pregnant women of severe mental illness and substance misuse leads to intrauterine death, increased risk of congenital defects, cardiovascular and musculoskeletal anomalies and foetal alcohol syndrome, all attributable to the misused substances (McElhatton *et al*, 1998, 1999). Drug and alcohol misuse in pregnancy is not considered in this review.

Antidepressants
Tricyclic antidepressants

Tricyclic antidepressants have been in use for several decades and have been prescribed extensively. Clinical observation and data support the safety of both tricyclic and tetracyclic anti-depressants. Animal studies with different tricyclics (for example imipramine, amitriptyline and dothiepin) and tetracyclics (for example maprotiline) using supramaximal doses have shown no increased risk of congenital malformations in first-trimester exposure (Altshuler *et al*, 1996). Case series studies of women who received imipramine and amitriptyline throughout all three trimesters of pregnancy concluded that tricyclics do not increase the risk of malformation (Crombie *et al*, 1972).

A statistically rigorous study by the European Network of Teratology Information Services (ENTIS) investigated the outcome of pregnancy in 689 women exposed to therapeutic dosages of antidepressants, including 283 women taking tricyclics from the first trimester onwards, and reported that there was no increase in malformation in the infants (McElhatton *et al*, 1996). Nulman *et al* (1997, 2002) found no increase in anatomical or behavioural teratology or later behavioural problems in children born to mothers taking tricyclics or fluoxetine during pregnancy. Nevertheless, there are some documented reversible perinatal complications in the form of withdrawal symptoms, mainly irritability, eating and sleeping difficulties and convulsions (Wisner *et al*, 1999; Nordeng *et al*, 2001; Simon *et al*, 2002), especially when tricyclics and fluoxetine have been used in high dosages and in the third trimester.

Selective serotonin reuptake inhibitors

There are several prospective studies, compiled databases and meta-analytic reviews on the effects of selective serotonin reuptake inhibitors (SSRIs) on the foetus. Fluoxetine (Pastuszak *et al*, 1993; Nulman *et al*, 1997, 2002; Ericson *et al*, 1999; Addis & Koren, 2000), paroxetine, sertraline, fluvoxamine and citalopram (Kulin *et al*, 1998; Ericson *et al*, 1999; Wisner *et al*, 1999; Nordeng *et al*, 2001; Simon *et al*, 2002) showed no increase in the incidence of major malformations of the infant at birth compared with non-exposed controls. In addition there was no increase in irreversible perinatal complications following late-trimester exposure to tricyclics or fluoxetine.

The question of an increase in spontaneous abortion rates of 13.3% (Goldstein, 1995) is important. Time will show whether there is a trend in spontaneous abortion following SSRI treatment. When establishing the risk of spontaneous abortion or malformations, the effects of alcohol, cigarette smoking and the possible unreported use of other medication, including benzodiazepines, analgesics and illicit drugs, should be also be considered.

According to Heath & Yonkers (2001), the manufacturer of citalopram has stated that no malformations in foetusus exposed to the drug have been reported, but it advises caution in its use during pregnancy. There is limited published research on the incidence in humans of teratogenicity or side-effects in the usage of trazodone, nefazodone and mirtazapine. Venlafaxine has been used in 150 pregnant women without an increase in the rates of major malformations above the baseline rate of 1–3% (Einarsen *et al*, 2001). Although there are single published cases showing absence of side-effects, caution should be exercised when prescribing novel antidepressant drugs to pregnant women.

Monoamine oxidase inhibitors

Traditional monoamine oxidase inhibitors (MAOIs), including tranylcypromine, phenelzine and iso-carboxazid, are drugs that require the adoption of a low-tyramine diet, and can initiate the 'cheese' reaction. Recently a selective reversible inhibitor of monoamine oxidase type A, moclobemide, a drug that requires a less restricted diet, has been introduced. These drugs are now used infrequently, owing to the development of safer and efficient newer antidepressants. There are few reliable reports on safety of MAOIs in pregnancy. It is therefore not advisable to start prescribing these drugs to pregnant women, even when all other possibilities have been exhausted. The practice should be to switch to safer antidepressants in the planning stages prior to pregnancy, and in un-planned pregnancies in the rare instances where the patient is taking MAOIs.

Commencing antidepressant treatment (Box 1) and maintaining it (Box 2) in pregnant women both need careful consideration.

Mood stabilisers

Lithium, carbamazepine and sodium valproate are established mood stabilisers in the treatment of mania and are also used in prophylaxis of bipolar affective disorder. Lithium has been in use for over four decades. Carbamazepine and sodium valproate are used successfully as anticonvulsants in people with epilepsy. These commonly prescribed drugs are known teratogens carrying an increased risk of malformations of the foetus.

If a woman is on maintenance treatment, the lowest possible dosage should be prescribed. If the woman needs to start taking a mood stabiliser, a conservative approach and high level of vigilance are advised.

Box 1 Commencing treatment of pregnant women with depression

- Discuss the treatment options with the patient and her carers
- Discuss the risks of remaining untreated and the risks and benefits of treatment to the child and the mother
- Start from the lowest possible dose and monitor frequently
- Assess the possibility of delaying the prescription until the second or even third trimester
- Look into alternative treatment possibilities

Box 2 General approach to treatment in pregnancy

- Once the decision has been made that the woman will need medication, try to avoid combination therapies in view of their greater potential for teratogenicity
- In the majority of cases, women who become pregnant while on medication need to be maintained on medication
- Maintenance strategies should involve dosage reduction and regular review of side-effects
- Discontinuation of mood stabilisers in pregnancy should take place only when absolutely necessary and be followed by frequent monitoring
- Midwives, obstetricians and health visitors should be involved in the discussion and should be informed of the risks and benefits
- Risk of recurrence increases in women who discontinue mood stabilisers

Lithium

Lithium is an effective mood stabiliser taken throughout pregnancy by many women with severe mood swings; nevertheless, it carries the potential of toxicity to the mother and serious teratological risks to the child if not appropriately monitored at every stage of pregnancy (Box 3). Lithium in pregnancy has a revised teratogenic risk based on meta-analysis of 0.05% and a relative risk 10–20 times that for the general population (Cohen *et al*, 1994). In the first trimester exposure to lithium may bring risk of malformation. Congenital cardio-vascular defects and different cardiac malformations of all types were increased in foetuses exposed to lithium in the first trimester of gestation (Kallen & Tandberg, 1983). Lithium can also cause foetal toxicity in the form of hypotonia, lethargy, poor reflexes, cardiac arrhythmias and difficulties in respiration. These are reversible and do not cause any later complications. Evidence based on prospective studies suggests that the risk to the foetus of lithium exposure might have been overestimated and the risk to the mother and child of lithium withdrawal might have been underestimated (Viguera *et al*, 2000).

Discontinuation of lithium is a complex issue. It is well documented that relapse may follow abrupt discontinuation in anyone having lithium treatment. Recurrence rates average up to 50% within 6 months of discontinuing lithium, and rapid discontinuation appears to increase risk of relapse even further, regardless of whether the patients are pregnant of not (Baldessarini *et al*, 1996; Viguera *et al*, 2000); the risk of relapse in pregnant women who discontinue the drug over a period of more than 4 weeks is not known.

Discontinuation of maintenance treatment is an important decision and should be made after discussion with the patient, her family and everyone involved in her care.

Carbamazepine

Carbamazepine is associated with different malformations: there is a 0.5–1% risk of spina bifida, craniofacial anomalies, microcephaly and growth retardation. Although neurobehavioural differences in exposed children were negligible, decreased average head circumference was noted (Scolnik *et al*, 1994).

Valproate

Prenatal valproate exposure has been associated with congenital anomalies, growth retardation, hepatotoxicity and foetal distress. Valproate carries the risk of spina bifida, craniofacial anomalies, digit and limb defects, heart defects, urogenital malformation, psychomotor slowness and low birth weight. According to Briggs *et al* (1994), the risk of neural tube defect is 1–2%; Koch *et al* (1996) reported a 10-fold increase in the risk of spina bifida. Koch

Box 3 Lithium treatment programme

- In women on maintenance treatment, serum lithium levels should be monitored every 4 weeks throughout the pregnancy
- Lithium dosage should be adjusted to match the lower end of the therapeutic range
- Lithium should not be discontinued abruptly; prior to delivery the dosage should be gradually tapered to 60–70% of the original maintenance level
- Lower doses and frequent blood monitoring should be the norm in pregnant women starting lithium in the first trimester of pregnancy
- Lithium commenced in the second and third trimester of pregnancy or in the perinatal period can help reduce the risk of puerperal psychosis
- Breast-feeding is not compatible with lithium treatment and women should be made aware of this prior to delivery
- Guidelines should vary with the severity of the illness
- No decision is risk-free

et al also examined the relationship between maternal anti-epileptic therapy, neonatal behaviour and later neurological functions and found that children exposed to valproate *in utero* showed neurological dysfunction and increased excitability in infancy and later. In the same study, valproate concentration in the infant at birth was found to correlate with degree of neonatal hyperexcitability and neurological dysfunction at age 6 years. Thus, valproate clearly leads to cerebral dysfunction in addition to malformations. Clayton-Smith & Donnai (1995) reported that the risk of congenital heart defect is increased 4-fold. A foetal valproate syndrome has been described (Clayton-Smith & Donnai, 1995).

The teratogenic potential of other anti-epileptic agents such as lamotrigine, gabapentin and topiramate, which at times have been used as mood stabilisers, is not well documented and remains unclear.

Antipsychotic medication

Conventional antipsychotics

Reports of the effects of psychotropic medication on the foetus first came from large studies in which psychotropic drugs were prescribed at low dosage as anti-emetics. Later animal studies and clinical observational publications on conventional antipsychotics, which have been in use for almost half a century, have shown that generally there is no increased teratogenic risk with high-potency conventional antipsychotics (van Waes & van de Welde, 1969; Kopelman *et al*, 1975; Wisner & Perel, 1988). The California Child Health Development Project (1959–1966) studied 19 000 births and found no significant increase in congenital abnormalities following prenatal exposure to oral or injectable antipsychotics (Slone *et al*, 1977).

Studies on phenothiazines in general and chlorpromazine in particular have concluded that there is no increase in morphological or developmental abnormalities associated with that treatment (Ananth, 1975; Wisner & Perel, 1996). Low-dose haloperidol in the first trimester of pregnancy has no detrimental effect on the weight of the foetus, the length of pregnancy, foetal or neonatal mortality or incidence of malformations (Van Waes & Van de Velde, 1969). No oral and depot conventional antipsychotic has been associated with teratology in the foetus, and it has therefore been concluded that these drugs are safe in pregnancy.

Sacker *et al* (1996) and Bennedsen (1998) completed a meta-analysis of all studies examining the complications of offspring of women with schizophrenia. They found that, although the effects were small, women with schizophrenia had an increased risk of pregnancy and birth complications. Low birth weight, preterm birth and perinatal infant death were more frequent. Since the incidence of poverty, smoking, substance misuse, violence and many other risk factors are increased in people with schizophrenia, the higher frequency of some complications could be attributed to these environmental factors.

Although it is beyond the scope of this review to cover research into the risks of schizophrenia, neuro-motor dysfunction and behavioural problems have been associated with maternal diagnosis of this disorder (Bergman *et al*, 1997; Amminger *et al*, 1999) and could be independent of medical treatment.

Atypical antipsychotics

Information on the prenatal use of the atypical anti-psychotics is based on single case studies and data collected by the pharmaceutical industry. There is a growing number of reported cases of women completing their pregnancy while taking clozapine, olanzapine, risperidone or quetiapine without any detrimental effects to the newborn (Miller, 1991; Tekell, 2001; Viguera & Cohen, 2002). The lack of any reported sequelae, although reassuring, needs to be replicated in larger and more rigorous studies to confirm the safety of these drugs in pregnancy.

Case reports on clozapine use in pregnancy have not suggested an increase in malformations, but there are concerns about hypotension, deficiency in knowledge regarding the prenatal and neonatal risks for agranulocytosis, and lack of foetal white cell measurements during pregnancy.

Reports on olanzapine-exposed pregnancies showed the lack of any associated teratogenesis. However, they drew attention to the importance of contraception for women who at any time change from conventional to atypical antipsychotics, as the high prolactin levels and lack of ovulation that accompany the conventionals are not produced by the atypicals, and therefore unplanned pregnancies may result from the switch.

I am not aware of any published case study in which amisulpride has been used during pregnancy; however, in view of the lack of reliable data its use is not advised during pregnancy.

Generally it is fair to say that conventional antipsychotics do not seem to pose a risk in labour and the perinatal period (Tekell, 2001). Complications in the infant are usually seen in the immediate postnatal period. Transient perinatal syndrome, floppy infants, withdrawal symptoms such as increased irritability, hypotonicity and hypertonicity, and underdeveloped reflexes have been persistently noted in infants who have been exposed *in utero* to different doses of mainly low-potency antipsychotics (Desmond *et al*, 1969; Hauser, 1985).

Box 4   Treatment of schizophrenia in pregnancy

In the case of women with pre-existing mental illness who plan to conceive:

- The patient should be included in the assessment of risks and benefits of continuation *v.* cessation of psychotropic treatment
- Women taking novel antipsychotics with limited safety data should consider switching to conventional medication
- Women successfully treated with psychotropic medication but facing difficulties in conceiving might try a period at a greatly reduced dosage or switching to a psychotropic drug that does not raise prolactin levels.

There should be no ambiguity in the decision to treat a pregnant woman with schizophrenia during pregnancy, because the risks associated with remaining untreated are very high (Miller, 1991). Therefore, although the consensus is to use antipsychotics at every stage of pregnancy, avoiding polypharmacy, using the lowest possible dosage, regular psychiatric and obstetric monitoring and review of medication are important (Box 4).

Anticholinergic drugs

Anticholinergic drugs have been frequently used in combination with conventional antipsychotics but their effects have not been widely studied. Nevertheless there are reports of possible teratogenicity associated with the use of anticholinergic drugs in combination with antipsychotics (Wisner & Perel, 1988). The consensus is that they should be avoided when possible and should be used in the lowest possible dosage when necessary. There are no studies that would help to differentiate between the effects of the most commonly prescribed anticholinergics.

Beta-blockers used during pregnancy, usually for akathisia, are not associated with any increase in congenital malformations (Rubin, 1981).

Benzodiazepines and pregnancy

Benzodiazepines are anxiolytic agents with a potential for misuse and dependence. All patients taking these drugs will experience withdrawal symptoms if treatment is discontinued abruptly. Benzodiazepines used in the first trimester have been linked to increased risk of up to 0.6% of oral cleft and congenital malformations of the central nervous system and the urinary tract (Altshuler *et al*, 1996). Wisner & Perel (1988), in their review of the pharmacokinetics of benzodiazepines in pregnancy, show that these drugs produce neonatal toxicity such as withdrawal symptoms in infants and may be the cause of respiratory depression and muscular hypotonia, leading to the diagnosis of floppy infant. However, dosages, duration of treatment, class of the drug and exposure to other concurrent drugs need to be taken into consideration. The general advice is that it is important to avoid high doses and long-term treatment. If for any reason the patient needs to be sedated, other, safer agents should be used.

Conclusions

The reproductive safety of psychotropic medication is an ongoing issue of great importance. Although the effects of medical treatment on the pregnant mother and the foetus are of major concern, the effects of remaining untreated and its possible impact on the foetus, and later on the infant, and the definite increase in relapse rates in the mother cannot be ignored. At this stage psychiatrists need to balance the relevant information, including clinical data and especially severity of illness, in their risk–benefit assessments. Wider consultation and trained staff recognising possible side-effects will contribute to the process.

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Multiple choice questions

1 The decision whether to use psychotropic medication in pregnancy should take the following into consideration:
a neonatal toxicity
b teratogenic risk
c hypotonia in the infant
d severity of the affective disorder
e risk–benefit assessment.

2 The risks of untreated mental illness in pregnancy:
a are quite well established
b impinge on the well-being of the mother and the infant
c include the possibility of neglect of the infant
d do not include low birth weight of the infant
e should deter women from getting pregnant.

3 The risks of discontinuing maintenance psychotropic medication in pregnancy:
a are negligible
b are not associated with relapse
c are decreased by gradual discontinuation
d include suicidal behaviour
e include poor prenatal care.

4 The data on reproductive safety are as follows:
a benzodiazepines are associated with oral clefts in 10% of newborns
b lithium is completely safe
c haloperidol does not carry a significant risk of teratogenicity
d clozapine can be safely used in all pregnant women
e there are not sufficient data on the atypical antipsychotics.

5 Antidepressants taken during pregnancy:
a can be beneficial in the treatment of depression
b can cause perinatal withdrawal symptoms in the infant
c have an unacceptably high risk of minor foetal abnormalities
d have a definite association with long-term neuro-behavioural problems in the child
e are linked with a high incidence of congenital malformations.

MCQ answers

1		2		3		4		5	
a	T	a	T	a	F	a	F	a	T
b	T	b	T	b	F	b	F	b	T
c	T	c	T	c	T	c	T	c	F
d	T	d	F	d	T	d	F	d	F
e	T	e	F	e	T	e	T	e	F