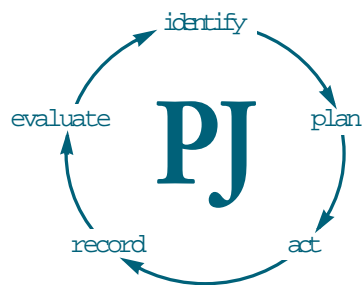


(3) DRUG USE IN PREGNANCY: PART 2

By Patricia R. McElhatton, PhD

This article focuses on epilepsy and thyroid disorders in pregnant women and the risks presented by these conditions, and their treatments, to both the mother and the fetus



identify gaps in your knowledge

1. Why is administration of vitamin K to pregnant women taking antiepileptic medication sometimes necessary?
2. Are there any guidelines for managing epilepsy in women of childbearing age?
3. What are the risks and benefits of treating hyperthyroidism in a pregnant woman?

This article relates to the Royal Pharmaceutical Society's core competency of "appropriate advice, referral or selection of treatment" (see "Medicines, ethics and practice — a guide for pharmacists", number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.

The care of the pregnant woman and her developing baby is one of the paradoxes of modern obstetric medicine. A healthy woman with an uneventful pregnancy will require little intervention. However, women with health problems, either pre-existing or that develop during pregnancy, and that might damage their own health or that of their baby may require appropriate use of diagnostic tests and prescribed medicines. It is important to balance the risks to the fetus associated with treating the maternal illness against the risks to both the mother and fetus of failing to treat the mother.

The first part of this article, published last week, looked at hypertension, diabetes and depression. In this second part the risks of epilepsy and thyroid disorders and their treatments are discussed.

EPILEPSY

The incidence of epilepsy in the general population is 0.6–1 per cent and about 40 per cent of people with epilepsy are women of child-bearing age. Approximately 3,000 to 5,000 infants are born to women with epilepsy each year in the United Kingdom and most of these infants will have been prenatally exposed to antiepileptic drugs. It is well known that women with epilepsy are at a greater risk of having a child with a major or minor congenital malformation^{1,2} than women without epilepsy (10 per cent vs 2–3 per cent).

In some pregnant women, seizure frequency can increase. Possible causes include hormonal changes, sleep deprivation and changes in antiepileptic drug clearance and binding. Data on whether or not maternal fits during pregnancy have any impact on the frequency of malformations are equivocal, but frequent and prolonged maternal fits can cause miscarriage, intracranial haemorrhage in the mother

and premature labour. In extreme cases, alterations in placental blood flow and transfer of oxygen and nutrients to the fetus can result in fetal hypoxia with bradycardia and brain damage. Therefore, it is important that antiepileptic therapy is continued throughout pregnancy and good seizure control is maintained.¹

There is no ideal epidemiological technique to separate the effects of the drugs and the effects of the disease itself on the fetus. Multiple drug regimens are associated with a greater risk, but this could be related to the severity of the maternal epilepsy. Overall, pregnant women on antiepileptic drugs still have a 90 per cent chance of having a normal baby.

Antiepileptic drugs Barbiturates, carbamazepine, oxcarbazepine, phenytoin, primidone, succinimides and valproate have all been associated with fetal malformations. These include anencephaly (lack of brain and bones at the back of the skull) and spina bifida, cardiac defects, hypospadias (abnormality in the penis where the urethra opens on the underside), limb abnormalities and facial dysmorphisms (eg, widely spaced eyes, depressed nasal bridge, cleft lip and palate, small jaw, low set ears, low hair line). In addition, these infants are often premature, hypoxic, growth retarded and have difficulty feeding. There is also a higher incidence of seizures, perinatal, neonatal and infant death, and developmental delay.

There are insufficient data in human pregnancy on the effects of monotherapy with the newer antiepileptic drugs such as gabapentin, lamotrigine, levetiracetam, topiramate and vigabatrin to give an adequate estimation of the risk of fetal toxicity. The manufacturer of lamotrigine has set up a registry to monitor pregnancy outcome data which, to date, look encouraging.

Folic acid Antiepileptics can cause folate deficiency and this has been proposed as a possible cause of teratogenesis. There are conflicting views as to whether folic acid should be added to food and whether folic acid supplementation before conception is effective in reducing the total incidence of congenital malformations.^{1,2} The results of the Medical Research Council trial in 1991 indicated that for women who have already had a child with a neural tube defect,

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PANEL 1: CONSIDERATIONS FOR WOMEN WITH EPILEPSY WANTING TO HAVE A BABY

- Women should be given preconception counselling about the risks
- Risks of fetal toxicity are related to duration of exposure before and during pregnancy
- Women should be referred to a neurologist and/or an obstetrician to reassess treatment
- Doses may need adjusting
- Peak drug levels should be reduced by increasing dose frequency if this does not interfere with seizure control
- Multiple drug therapy is associated with an increased risk of fetal malformation
- Folic acid (5 mg daily) should be taken up to week 12 of pregnancy

preconception supplementation with folic acid reduced the recurrence risk of neural tube defects such as spina bifida.³ All pregnant women are now advised to take folic acid 400µg daily during the first three months of pregnancy, when the fetal major organs are forming. Women who have a family history of malformations or who are in a high risk category (eg, suffer from epilepsy) are recommended to take the higher dose of 5mg daily prior to conception and during the first three months of pregnancy.

Vitamin K Vitamin K is needed so that the liver can produce blood clotting factors (eg, prothrombin) and in the production of some of the proteins needed for bone development. Some antiepileptic drugs (eg, carbamazepine, phenobarbital, phenytoin, topiramate) induce liver enzymes and reduce the levels of vitamin K.^{1,2} Infants are relatively deficient in vitamin K and prenatal exposure to these antiepileptics has been reported to cause neonatal bleeding, usually in the first 24 hours after delivery.

There is some placental transfer of vitamin K from the mother to the fetus but the mechanism is not well defined. Vitamin K supplementation is recommended to prevent intracranial bleeding in the neonate. A commonly used regimen is to give an oral daily dose of 20mg vitamin K to the mother from the 36th week of pregnancy and usually 1mg vitamin K to the newborn at birth, either orally or intramuscularly. The fetal dose is repeated after 12 hours. Evaluation of the prothrombin times and levels of vitamin K-dependent clotting factors should be performed.

Epilepsy management Although there have been a number of local initiatives to develop guidelines for the treatment of epilepsy in women of childbearing age, national agreement is lacking. The guidelines used by the National Teratology Information Service are compiled from the published data available and from discussions with relevant clinical experts. Panel 1 shows measures that should be considered for women with epilepsy before conception. Panel 2 shows measures that should be considered during pregnancy.

THYROID DISORDERS

The thyroid is the first endocrine gland to develop in the fetus, at about week three or four post conception, with follicles growing and colloid being produced at 10 to 12 weeks. By the end of the third month of pregnancy the gland will have begun to function.

Maternal thyroid function changes during pregnancy in response to changes in protein binding, hormone production and an increased need for iodine. Both overactivity (hyperthyroidism or thyrotoxicosis) and underactivity (hypothyroidism) of the maternal thyroid gland can have adverse effects on fetal development.

Hyperthyroidism Hyperthyroidism affects up to 0.2 per cent of pregnancies and if left untreated is associated with increased fetal mortality and morbidity. Thus treatment with antithyroid drugs such as propylthiouracil or carbimazole is required. Beta-blockers, such as propranolol, should be reserved for pre-surgical treatment and immediate control of severe thyrotoxic features.^{2,4-6}

PANEL 2: MEASURES RECOMMENDED FOR PREGNANT WOMEN WITH EPILEPSY

- Good antenatal care is required
- Appropriate antiepileptic medication should be continued to avoid fits
- If the epilepsy is well-controlled, current medication should be maintained
- A dating scan should be performed at 12 weeks
- An alpha-feto-protein test can be performed at 16 weeks' gestation because it can assess the risk of spina bifida
- An ultrasound scan should be performed at 20 weeks gestation because it can detect spina bifida (90 per cent) and major cardiac malformations (25 per cent)
- Amniocentesis and other specialised tests should be performed as required

However, there is considerable concern among health care professionals about the potential adverse consequences of maternal antithyroid treatment for the fetus, and sometimes conflicting or inappropriate advice is given.

There are two main concerns. First, these drugs cross the placenta and can sometimes cause hypothyroidism and goitre in the fetus. However, adverse effects on fetal thyroid function are unlikely unless treatment begins after 10 weeks' gestation when the fetal thyroid is functional. In two studies in which antithyroid therapy was used in moderate doses and maternal thyroxine concentrations were maintained at the upper end of the normal range, maternal and fetal outcome was satisfactory regardless of the antithyroid drug used.⁷ Close monitoring of thyroid function, approximately once a month, is particularly important because the need for antithyroid therapy often declines through pregnancy, and in the second trimester treatment may occasionally be discontinued.

There have been no suggestions from recent studies that antithyroid therapy has adverse effects on fetal thyroid size or function, or on subsequent physical or intellectual development, as occurs in congenital hypothyroidism. There is equivocal evidence suggesting that placental transfer of propylthiouracil may be less than that of carbimazole so this drug may be the least likely to damage the fetal thyroid. Carbimazole also presents a risk of neutropenia and agranulocytosis and in such cases, according to advice from the Committee on Safety of Medicines, treatment should be stopped immediately.

The use of higher doses of carbimazole in combination with thyroxine to prevent hypothyroidism (blocking-replacement therapy) should be avoided in pregnancy. There is high placental transfer of carbimazole but not thyroxine, putting the fetus at risk of intrauterine hypothyroidism, even if the mother's thyroid function has been restored to normal (euthyroid). Also, congenital abnormalities are more common in the babies of women receiving thyroxine and carbimazole (9.5 per cent) than in those treated with carbimazole alone (4.1 per cent).

The second concern is that antithyroid drugs may have teratogenic effects. Several case reports described a scalp defect, aplasia cutis, in the infants of women taking carbimazole or methimazole (the active metabolite of carbimazole). Aplasia cutis is a congenital absence or deficiency of a localised area of skin with the base of the defect covered by a thin translucent membrane. Most often it occurs in a single area near the vertex of the scalp but it may occur in other areas and underlying structures may be affected. Inheritance is thought to be autosomal, either dominant or recessive. However, more recent systematic research reviewing nearly 50,000 pregnancies does not suggest that there is a high risk of aplasia cutis from exposure to antithyroid drugs.⁸ In a recent study of 643 neonates born to mothers with Graves disease there were no cases of aplasia cutis and congenital malformations were significantly more common in the offspring of women whose hyperthyroidism was left untreated (3/50 = 6 per cent) compared to those receiving methimazole (3/593 = 0.5 per cent).⁹ In 2001 there were a few case reports of choanal atresia (the airway between the nasal and pharyngeal areas is blocked by bone and membranous tissue), oesophageal atresia (the

oesophagus is blocked by bone and membranous tissue), hypoplastic nipples and psychomotoric developmental delay following fetal exposure to methimazole. However, data from a prospective controlled study by the European Network of Teratology Information Services (ENTIS) on 229 pregnancies exposed to methimazole reported nine malformations among them only one of choanal atresia and one of oesophageal atresia.¹⁰

Radioiodine administration also raises a number of concerns.⁶ For hyperthyroidism, the usual dose range of radioiodine is four to 10 millicuries (mCi; unit of radioactivity), depending on the patient's condition. As the fetal thyroid is able to concentrate iodine from about 10 to 12 weeks' gestation, radioiodine administered later than this may cause ablation of the gland, resulting in fetal and neonatal hypothyroidism with potentially severe and irreversible consequences, including mental retardation.

Parental gonadal exposure may result in genetic effects and several studies have demonstrated chromosomal damage following radioiodine. However, the increased risk of genetic abnormalities arising from this exposure is low (0.003 per cent) compared with the spontaneous risk of genetic abnormalities in the general population under 35 years of age (0.8 per cent). Studies in Japanese atomic bomb survivors, and in the offspring of those treated with high doses of radioiodine for thyroid cancer, have demonstrated little evidence of genotoxicity and do not suggest that patients who have received radioiodine before conception produce abnormal children. Nevertheless, an interval of at least four months is normally advised between maternal radioiodine therapy and conception and some also apply this interval to a prospective father.

The risk to the fetus of cancer or heritable disease caused by treatment with radioiodine has been estimated at one in 15,000 to 20,000 per mGy (milligray; a measure of the radiation energy absorbed). In early pregnancy, although the risk of cancer induction is not zero, it is lower than at later stages of pregnancy, probably because at later stages cells have become specialised and damage is more likely to be permanent. Despite the possible risks associated with radiation to the fetus, inadvertent therapy with ¹³¹I radioiodine does not always adversely affect the fetus if radioiodine is administered before the 10th week of gestation. In patients who received radioiodine in higher doses (eg, for carcinoma of the thyroid) before conception there was also no increase in fetal malformation, although there was a slightly higher miscarriage rate that may have been due to a change in the maternal hormonal status.

The threshold doses for fetal death and fetal malformation are far in excess of those from "normal" radioiodine therapy for hyperthyroidism. If the irradiation occurs between eight to 15 weeks there is a chance that mental retardation could result regardless of the dose, but the predicted loss would be 0.03 intelligence quotient points per mGy, which is unlikely to be clinically important with antithyroid drugs.

The effects of maternal ¹³¹I radioiodine treatment on the fetal thyroid can be investigated by measuring fetal thyroid stimulating hormone through umbilical cord sampling and this may indicate the need for fetal thyroxine therapy. Unlike therapeutic doses in the range of mCi, diagnostic ¹³¹I is used in μ Ci, well below the dose that will impair fetal thyroid function.

Women exposed to antithyroid drugs or radioiodine in early pregnancy need accurate and timely information when deciding whether to proceed with the pregnancy. The best available evidence indicates that the risk to the fetus from exposure to these treatments in early pregnancy is low^{4-6,10} — lower than is commonly perceived, and less than that of untreated hyperthyroidism.

Hypothyroidism Hypothyroidism is usually associated with iodine deficiency, or autoimmune thyroiditis but may be due to iatrogenic effects as a result of thyroidectomy or ¹³¹I therapy. However, clinical diagnosis of hypothyroidism is often difficult. During pregnancy hypothyroidism can impair the mental development of the baby and adversely affect neuropsychological test results. An increase in miscarriages, stillbirths and congenital anomalies has also been reported. Therefore appropriate treatment is essential for both maternal and fetal wellbeing.

Thyroid hormones such as the L-tri-iodothyronine (T3), and thyroxine (T4) that are metabolically active in their free non-protein bound form are effective treatments. T3 is the more biologically

action : practice points

1. Think about how you would respond to a woman taking drugs for epilepsy and who is anxious about how this might affect her plans to have a baby.
2. Visit the National Society for Epilepsy website (www.epilepsynse.org.uk). Try the general quiz and look at the information available on pregnancy and child care.
3. If necessary, revise your knowledge of thyroid disorders. For example, take some time to read Martindale 33, pp1519–21 or to visit Medline plus (www.nlm.nih.gov/medlineplus/thyroid_diseases.html).

evaluate

How could your learning have been more effective?
What will you do now and how will this be achieved?

effective hormone with a short period of activity whereas T4 is the less effective prohormone that needs to be deiodinated to T3 as required. Thyroid hormones are essential for placental development, but placental transfer is limited. However, where fetal thyroid agenesis occurs there is substantial transfer of maternal T4 because of the high concentration gradient.

There is no evidence of an increased risk of congenital anomalies following the use of either T3 or T4. As for other people with hypothyroidism, when thyroid hormones are required for pregnant women T4 preparations should be used so that the patient retains control over the hormonal activity by controlling the conversion of T4 to T3. The dose of T4 is variable, depending on the severity of the underlying disease. Requirements may increase during pregnancy. Therefore, regular monitoring of blood levels during pregnancy to ensure adequate thyroid control is recommended. T3 is reserved for severe hypothyroid states. Iodine should be supplemented as required, but it is important to get the balance right.^{5,6,10} Low iodine levels are associated with cretinism but if the mother takes too much iodine, fetal hypothyroidism can be induced.

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