NEUROLOGY AND MEDICINE

The neurology of pregnancy

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The neurology of pregnancy can be split into two. On the one hand, there are women who develop neurological symptoms *during* pregnancy. Some have simple neurological disorders such as carpal tunnel syndrome, which are more common during pregnancy. Others have disorders that are either peculiar to or very much commoner during pregnancy, such as eclampsia, pelvic neural compression, or even tumours arising from the placenta. The most common, serious, and important of these conditions is eclampsia. Other women have neurological problems such as epilepsy or myasthenia first and then become pregnant. For these patients, pregnancy may affect the course of the disease, and there may be important issues with respect to investigation, treatment, and prognosis.

Eclampsia

Eclampsia is one of the commonest causes of maternal death. In the United Kingdom, recent figures show that 15.5% of direct maternal deaths were due to the hypertensive disorders of pregnancy, and more than half of these women had eclampsia.[1] As many as 50 000 maternal deaths annually world wide are thought to be as a consequence of eclampsia.[2] The incidence of eclampsia during a recent nationwide survey in the United Kingdom was about one in 2000 maternities, with a case fatality ratio of almost one in 50.[3] We do not know how many women presenting with the fulminating features described below will go on to have convulsions, or whether drug treatment can reduce the chance of progression. In one observational study, only one in 75 women with severe pre-eclampsia developed eclamptic convulsions.[4]

DEFINITIONS

Pregnancy induced hypertension (also known as pre-eclampsia and pregnancy toxaemia) develops after 20 weeks of gestation in previously normotensive women and resolves by three months postpartum; the pressure is considered raised if greater than 140/90 mm Hg, or if the diastolic blood pressure rises 15–25 mm Hg above prepregnancy values.[5] When such a patient has a convulsion, they should be considered to have eclampsia unless proved otherwise. Such patients are likely also to have significant proteinuria (>0.5 g/24 hours, or at least + with urine dipstick testing), facial or generalised oedema, and symptoms of headache, visual disturbances (typically photopsia), epigastric pain, or vomiting. This prodromal state is typical, but the convulsions of eclampsia may arise apparently unheralded and at what seems to be normal blood pressure. Eclampsia is most common during the third trimester of pregnancy or during labour, but can also occur after delivery, typically within the first 48 hours.

PRODROMAL FEATURES AND DIAGNOSIS

Certain clinical features, indicating pre-eclampsia of significant severity, are typical in patients who subsequently develop generalised convulsions. It is difficult to know whether and over what time scale this progression may occur in an individual patient. Such patients typically have high and rapidly rising or extremely labile blood pressure, proteinuria (sometimes in the nephrotic range), visual disturbances (especially photopsia or cortical blindness), headache, malaise, new onset of peripheral oedema (especially periorbital or facial), oliguria, restlessness, shivering, and clonus. Laboratory evidence of multisystem disease (such as hyperuricaemia, thrombocytopaenia, raised liver enzymes, or haemolysis) is also common.

Other patients fail to show these warning signs and clinicians may not recognise impending eclampsia or may even fail to make the diagnosis when convulsions ensue. Examples include patients who present during the second trimester of pregnancy or in association with molar degeneration of the placenta. In other cases the prodromal features are distracting, such as predominantly epigastric pain and vomiting, rather than headache and visual disturbance. The diagnosis may also be missed when patients present in labour or the early puerperium, when the blood pressure has always been normal (but beware rapidly rising blood pressure or onset of proteinuria peripartum). In other cases the blood pressure may not be particularly raised or else there may be no information about the patient's "normal" prepregnancy blood pressure. Sometimes the patient or her medical attendants do not know that she is pregnant; other times the convulsions begin late in the puerperium (>48 hours after delivery). Rarely, in an obtunded patient, the seizures may not have been witnessed.

Important differential diagnoses in a pregnant woman having her first seizure are intracerebral (particularly subarachnoid) haemorrhage and cerebral venous thrombosis. Other

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possibilities are tumours, intracerebral infection, metabolic disturbances, and autoimmune disorders (particularly systemic lupus erythematosus).[6]

PATHOPHYSIOLOGY

It is always difficult to know how best to treat or prevent a disease when its underlying pathophysiology is incompletely understood. Our understanding of the cerebral changes occurring in pre-eclampsia and eclampsia has changed with the improvement of neuroradiological techniques. The traditional view was that eclampsia was due to intracerebral haemorrhage, because that is what was typically found postmortem.[6] Yet proposed pathophysiological mechanisms must provide explanations for several clinical findings: firstly, that eclamptic convulsions can arise suddenly in a patient with little or no prodrome; secondly, that eclampsia does not always occur with extremely high blood pressure or prolonged increase in blood pressure; and thirdly, that there may be transient focal neurological defects (such as cortical blindness or hemiparesis) yet most women who survive eclampsia do so neurologically intact.

It has variously been proposed that eclamptic convulsions result from intracerebral haemorrhage, hypertensive encephalopathy, cerebral oedema, or cerebral vasospasm.[6 7] Different mechanisms may be operating in different patients, with the compounding effects of cerebral hypoxia, intravenous fluid and drug administration, and varying degrees of hypertension. The women who die are likely to be at the worst end of the range. Those who die of eclampsia have significantly higher blood pressure, but no worse renal function or more proteinuria than those who survive.[8]

Typical postmortem cerebral findings are fibrinoid necrosis of vessels, thrombosed precapillaries, perivascular ring haemorrhages, subarachnoid, intraventricular, and intracerebral haemorrhages (including patches of petechial haemorrhage in the cerebral cortex), hypoxic-ischaemic damage, and perivascular microinfarcts.[6 7 9 10] Studies with CT have shown that eclamptic patients with evidence of cerebral haemorrhage are likely to die as a consequence of their condition;[10 11] such patients may have a profound coagulopathy. Surviving patients are more likely to have either normal scans or patchy, low density areas.[11]

Generalised cerebral oedema has been documented in eclampsia postmortem,[6 7] found on CT in unconscious eclamptic patients,[12] and has been suggested in patients in whom intracranial pressure was directly monitored and found to be raised;[10] but it is not a universal finding.[9 11] Many such patients may have iatrogenic fluid overload or oedema may be a consequence of prolonged cerebral ischaemia. Other studies have found the brain in pre-eclampsia and eclampsia to be of similar weight[9] or even smaller[13] than normal.

Brain MRI may identify abnormalities where CT has failed to do so. The characteristic neuroradiological features of severe pre-eclampsia and eclampsia are hypodense lesions on CT which show increased T2 signals on MRI.[14–17] Abnormalities are more common in patients with eclampsia.[16] There is a predilection for abnormalities in the occipital and parietal lobes, in the watershed area between middle and posterior cerebral artery territories.[15 16] The distribution of lesions shows good correlation in most cases with the patient's clinical features, such as occipital pole lesions in women with cortical blindness.[14 15] Enhancement of T1 signals after injection of gadolinium has been documented in regions with increased T2 signals.[17] The lesions are interpreted as indicating areas of abnormal water content—that is, focal cerebral oedema. There is much debate about whether such oedema is intracellular, indicating areas of focal ischaemia, or whether it is extracellular, secondary to capillary leakage and breakdown of cerebral autoregulation.[14–17]

It is, however, important to determine which is the more important mechanism, as this will determine pharmacological strategies to ameliorate or prevent eclampsia. The proponents of the breakdown of cerebral autoregulation theory argue that eclampsia is simply hypertensive encephalopathy and that the keystone of treatment should be good control of blood pressure.[18] This leaves a dilemma in a patient with "normal" or only marginally raised blood pressure as to what should be the target blood pressure. If focal ischaemic areas develop as a consequence of cerebral vasospasm, then specific vasodilator agents are likely to be more beneficial and lowering blood pressure in some circumstances could further aggravate ischaemic processes.

An increasing body of evidence points to the presence of cerebral vasospasm in eclampsia and also in severe pre-eclampsia. Cases have been reported where cerebral angiography and magnetic resonance angiography,[19 20] performed after eclamptic seizures, have shown diffuse vasospasm. Similar images have also been noted in women with severe pre-eclampsia.[21 22] Follow up images documented resolution of vasospasm in association with clinical recovery. Is cerebral vasospasm a primary feature of eclampsia, causing focal or generalised ischaemic areas, which give rise to seizure foci and impaired neuronal function? Or, is the vasospasm a secondary phenomenon, protecting the brain from the damaging effects of raised arterial pressure?

In experimental hypertension in animal models, pial arteriolar constriction has been directly observed, including a "sausage-string" pattern.[7] Cerebral blood flow is stable over a wide range of systemic arterial pressures. Once the upper limit of this autoregulation is achieved, blood flow increases. Damage occurs in capillaries, allowing escape of plasma proteins and blood cells into the perivascular spaces. This is the important pathophysiological basis of hypertensive encephalopathy.[7 18] These processes indubitably occur in some patients with eclampsia, particularly in those in whom high arterial blood pressure has persisted untreated for a considerable period of time. However, the concept that eclampsia is

simply hypertensive encephalopathy does not fit all the available facts.

Patients with pre-eclampsia and eclampsia exhibit increased sensitivity to vasoactive agents such as catecholamines and angiotensin II, and vasospasm has been proposed as the underlying mechanism causing multiple organ dysfunction.[5 23] Optic arteriolar vasospasm and nail bed vessel spasm are clinical features in some patients. Epigastric pain, of an angina-like quality, is a sinister feature which may herald eclamptic seizures. Some patients experience relief from epigastric pain after the administration of vasodilating drugs. Rapid improvement occurred in the neurological status of a woman with recurrent eclamptic seizures and MR evidence of widespread cerebral ischaemia, after administration of nimodipine, a cerebral vasodilator.[24] That abnormal electrical activity arises in ischaemic areas of the brain due to focal or widespread cerebral vasospasm is an attractive hypothesis. It explains the unpredictable nature of eclamptic seizures, their association with localising signs in some patients and non-specific features in others (headache, reduced conscious level etc), the potential for full recovery without neurological deficits or radiological signs, and the fact that seizures may occur with or without increases in systemic arterial pressure.

MANAGEMENT

A bitter debate has taken place about the optimal prophylaxis or treatment for eclampsia, between obstetricians and neurologists, and between practitioners from North America and those in the rest of the world.[18 25] Should management of eclampsia consist of giving anticonvulsant drugs (such as phenytoin) or antihypertensive agents? Would magnesium sulphate prove valuable if tested scientifically in a proper clinical trial against other agents? Fortunately, clinical studies have now provided answers to some of these questions, but other uncertainties remain.

A woman experiencing a generalised eclamptic convulsion should be managed initially with whatever anticonvulsant agents are to hand and with which a practitioner is familiar. The important thing is to terminate the seizure because both mother and fetus may become hypoxaemic if the fit is prolonged. The more difficult issue is whether drug therapy can be used to prevent eclamptic seizures in the first place or reduce the risk of recurrent seizures. Sedative anticonvulsant drugs (diazepam, barbiturates, chlormethiazole) have been used extensively in the management of patients with severe pre-eclampsia and eclampsia. However, heavy sedation does not necessarily prevent convulsions in these patients. Maternal respiratory depression caused by sedative agents can result in hypoxaemia and hypercapnia and possible aggravation of cerebral injury. Such patients are also at risk of aspiration pneumonia. Deterioration in the conscious state cannot necessarily be attributed to worsening of their clinical condition. Short term intravenous chlormethiazole has the advantage of being titratable against level of consciousness, but often involves administration of large volumes of fluid; a dangerous practice in an oliguric patient. For all these reasons, maintenance use of sedative anticonvulsants should be avoided.

Phenytoin was introduced in the 1980s as a good non-sedative anticonvulsant drug for the treatment and prevention of eclampsia.[26] However, with increasing use it has become apparent that eclamptic convulsions may occur despite plasma phenytoin concentrations in the therapeutic range.[27 28]

Magnesium sulphate has been the drug treatment of choice for eclampsia and pre-eclampsia in the United States for more than 80 years, although its initial use was on an empirical basis. Only recently have large studies compared its use with other agents (phenytoin and diazepam).[2 28] In a study of 1680 women with eclampsia,[2] those treated with magnesium sulphate had a 52% lower risk of recurrent convulsions than those given diazepam and a 67% lower risk of recurrent convulsions than those given phenytoin. In another study,[28] more than 2000 women who presented in labour with hypertension (blood pressure=140/90 mm Hg) were randomly allocated to treatment with either magnesium sulphate or phenytoin. Those who had already had eclamptic seizures were excluded, but otherwise the study had broad inclusion criteria. Hydralazine was used to control diastolic blood pressure that exceeded 110 mm Hg. The trial was discontinued when an interim analysis found that eclampsia developed in 10 of 1089 women given phenytoin prophylaxis, but none of 1049 women given magnesium sulphate.The authors noted that the expected incidence of eclampsia in similarly hypertensive women given magnesium sulphate prophylaxis, based on findings at their hospital over many years, was one in 750.

These studies yield persuasive evidence for the efficacy of magnesium sulphate in the management of women with severe pre-eclampsia or eclampsia, compared with phenytoin or diazepam. What should be borne in mind, however, is that there is a range of severity for the underlying condition ("pre-eclampsia" or "toxaemia") and that there is not the same risk of developing eclamptic convulsions in an asymptomatic woman with a blood pressure of 150/100 mm Hg as in another with the same blood pressure but also 2 g/24 hour proteinuria or another with escalating symptoms (headaches, vomiting, etc). Is it appropriate to give prophylactic treatment to women with mild and moderate degrees of pre-eclampsia, or should it be reserved for the more truly "at risk" group with severe increase in blood pressure and evidence of multiorgan disease (from symptoms or laboratory findings)? Not enough is known yet about whether magnesium sulphate reduces or enhances the survival chances of the fetus, which may be both premature and growth restricted.[5 7 29]

It is also difficult to know the relative importance of a particular pharmacological treatment (for example, magnesium sulphate) compared with other issues of management,

such as time taken to effect delivery of the fetus and control of blood pressure.[8] Women who die of severe pre-eclampsia or eclampsia do not all have intracerebral haemorrhage; some have adult respiratory distress syndrome, disseminated intravascular coagulation, or congestive heart failure.[1 3] Correct recognition of the condition, and involvement of experienced doctors in the management of women with severe pre-eclampsia or eclampsia is likely to be as important for the eventual outcome for mother and fetus as the actual drugs used. The development of special interest teams for the management of severe pre-eclampsia and eclampsia has been recommended after the recent confidential inquiry into maternal deaths in the United Kingdom.[1 8]

In pre-eclampsia, our own practice (modified from reference[30]) is to give 5 g magnesium sulphate intravenously over 20 minutes (by adding 10 ml 50% magnesium sulphate solution to 200 ml normal saline). We then infuse magnesium sulphate at 2 g/h. We measure the magnesium concentration after 30–60 minutes and then every six hours to maintain a therapeutic range of 2–3 mmol/l. If the blood pressure falls below 110/70 mm Hg, the respiratory rate falls below 16, urine output is below 30 ml/h, or areflexia occurs, we reduce the infusion rate to 1 g/h and measure the magnesium concentration urgently.

If patients have seizures on this regime, we take blood for an urgent magnesium concentration and give a further bolus of 2 g magnesium sulphate over two to three minutes. If fits continue after five minutes, we give a benzodiazepine.

One of the criticisms levelled against magnesium sulphate, before there was clear evidence for its efficacy in the management of eclampsia, was that it did not have true anticonvulsant properties.[7 18] Magnesium, however, has been shown to have vasodilator properties and it may be that its action in eclampsia is due to reduction in cerebral vasospasm.[25 28] If this is so, then other specific cerebral vasodilators including nimodipine deserve further investigation for the management of eclampsia.

CONCLUSIONS

Eclampsia is an uncommon condition in the developed world, but is associated with a disproportionate degree of maternal and fetal mortality.[3] For this reason, it is important to improve our recognition of patients at risk for the condition and their subsequent management. The report on the confidential enquiry into maternal deaths in the United Kingdom has a sobering chapter about how easily things can go wrong.[1] Each case of severe pre-eclampsia and eclampsia should be assessed individually and managed in a specialist unit according to carefully thought out protocols, dealing with issues such as fluid balance, seizure control, conduct of delivery, and anaesthesia. There should be clear guidelines for laboratory investigations, including radiological imaging and access to information allowing interpretation of the tests. Advice for those managing patients must be available from someone familiar with all the potential haematological, cardiovascular, renal, hepatic, and obstetric as well as neurological problems. "Treating the underlying cause" of the problems means expediting delivery of the fetus and placenta; other care is generally supportive in nature. It is important to ensure that iatrogenic problems such as fluid overload do not complicate recovery.[1 5] The signs of recovery are heralded generally by a spontaneous diuresis and lowering of blood pressure, ahead of improvement in measured haematological or biochemical factors.

Other neurological symptoms arising during pregnancy

Almost any medical disorder which can occur in a woman of childbearing age can occur during pregnancy. Most are probably no commoner than would be expected by chance. There are, however, neurological disorders which occur more commonly during pregnancy than at other times, or which demand special treatment at this time and some of these are briefly mentioned here.

MINOR NEUROLOGICAL DISORDERS

Several minor neurological disorders occur more often during pregnancy than at other times; Bell's palsy and the carpal tunnel syndrome are common examples.

The incidence of Bell's palsy is higher during pregnancy and the puerperium (38–45 women per 100 000 pregnancies *v* 17 per 100 000 women-years in non-pregnant women of childbearing age[31]). Recovery is usual. Some neurologists prescribe a short course of steroids if patients are seen early after the development of facial weakness (whether or not they are pregnant). Such treatment probably does no harm in pregnancy (see below), although the evidence that it is beneficial is by no means secure.[32–34] Rarely, patients have recurrent Bell's palsy in successive pregnancies.[35 36]

The carpal tunnel syndrome is also more common in pregnancy. Estimates of incidence vary between almost ridiculous extremes (1–50%). Conservative management is almost always appropriate because resolution after pregnancy is the rule,[37] although surgical treatment may be necessary[38] and the condition may recur in subsequent pregnancies. Not all pain in the hand during pregnancy is due to the carpal tunnel syndrome; de Quervain's tenosynovitis is also more frequent.[39] The incidence of meralgia paraesthetica is also increased. Conservative management is best. It may recur in successive pregnancies.[40]

GUILLAIN-BARRÉ SYNDROME

The Guillain-Barré syndrome is no more common in pregnancy than at other times[41]. Both plasma exchange[42] and immunoglobulin therapy have been used in pregnant patients with successful outcome. Fetal survival is usual. Rarely, the newborn child of an affected mother may also be affected.[43] The course of the maternal neuropathy is unaffected by termination or delivery.

STROKE IN PREGNANCY

Although it has been thought for many years that pregnant women carry a considerably increased risk for the development of stroke, a recent critical appraisal of the data suggested that the risk of ischaemic stroke due to presumed arterial occlusion may well have been exaggerated because of referral and selection bias.[44] In a recent retrospective case-control study of 497 women with "a reliable cerebral thromboembolic diagnosis", pregnancy only carried a small and non-significant increase in risk with an odds ratio of 1.3 (non-significant), in comparison to an odds ratio of 5.4 for diabetes, 3.1 for hypertension (both $p<0.001$), and 2.8 for migraine ($p<0.01$).[45]

When stroke does occur in pregnancy, it is as likely to be due to haemorrhage as to infarction, and there is an increase in the proportion of cases related to venous thrombosis (particularly in the third trimester and puerperium). In women with an unruptured arteriovenous malformation, the risk of a first haemorrhage during pregnancy is about 3.5%. This risk is no higher than over a similar period outside pregnancy.[46] We do not recommend surgery for arteriovenous malformations during pregnancy. About 1 in 10 000 pregnancies is complicated by rupture of an intracranial aneurysm.[47] Unruptured cerebral aneurysms are common, with an incidence of around 5%;[48] the risk of rupture of a previously asymptomatic aneurysm during pregnancy must be low, though this has not, to our knowledge, been formally studied. We do not recommend prophylactic surgery (for an incidentally discovered asymptomatic cerebral aneurysm) during pregnancy. When aneurysmal rupture does occur, the aneurysm should be operated on before delivery.[49] Aneurysmal rupture is more likely in the second and third trimesters (30% and 55% of ruptures respectively), than in the first trimester or puerperium (6% and 9% respectively).[50] In those women who do not require neurosurgery during pregnancy, caesarean section may not afford any better maternal or fetal outcome than vaginal delivery.[49]

For women who require anticoagulants during pregnancy, heparin (which does not cross the placenta) is generally preferable to warfarin. The only exception is in patients with prosthetic heart valves in whom heparin does not give sufficient anticoagulation and warfarin should be used until around 37 weeks of gestation[51] and then full dose heparin to term. Heparin carries a low risk of maternal osteopenia. Low molecular weight heparin has the advantages of sparing calcium and ease of use (it is given once daily as a subcutaneous injection). Daily aspirin in low dose (60 to 150 mg) has been used by obstetricians in the second and third trimesters without evidence of fetal harm.[52] The use of aspirin in the first trimester remains controversial because of uncertainty about whether it is teratogenic.[53 54]

NEOPLASTIC DISEASE

Most types of tumours have been reported in pregnant women, with the range of tumour types similar to those of non-pregnant women of similar age. There is probably no greater overall incidence of primary brain and spinal tumours in pregnant women than in age matched non-pregnant women.[55]

Gliomas

Management decisions in pregnant patients with gliomas are difficult. With low grade tumours, it may be possible to defer all treatment until after delivery whereas higher grade lesions often require surgical resection during pregnancy. Radiotherapy during pregnancy may cause abortion, mental retardation, and congenital defects[56] and chemotherapy may also lead to fetal malformations. Both are best deferred until after delivery. Steroids may be used when necessary (see below).

Pituitary tumours

Many (perhaps most) women with pituitary tumours are looked after by endocrinologists, rather than neurologists. In patients with microadenomas or presumed microadenomas measuring 1cm or less, the risk of developing visual loss after as many as four full term pregnancies is very small, whereas six of eight women with larger tumours ran into visual problems during pregnancy.[57]

Meningiomas

The hormonal effect of pregnancy, with high oestrogen leading to accelerated or even explosive growth of meningiomas, is well known. Even so, unless the tumour has reached a critical size such that serious neurological impairment is present or imminent, treatment can often be delayed until after delivery, by which time the tumour size and severity of symptoms may be reduced.[55]

Tumours peculiar to pregnancy

Choriocarcinoma is the commonest systemic cancer associated with pregnancy. It may follow a molar pregnancy, abortion, ectopic pregnancy, or term pregnancy. Brain metastases are common and untreated mortality is high. Survival is improved by early diagnosis and treatment; patients usually require chemotherapy and cranial radiotherapy.[58]

MOVEMENT DISORDERS BEGINNING IN PREGNANCY

Chorea gravidarum refers to chorea occurring during pregnancy. Recognised causes of chorea starting at this time include hereditary, drug related, immune, and vascular disorders. That chorea gravidarum is less common than it used to be is probably a reflection of the reduced incidence of rheumatic fever (Sydenham's chorea) due to the widespread use of antibiotics. Treatment may be unnecessary. If the chorea is disabling, haloperidol may provide the best balance between efficacy, mild teratogenesis, and propensity to induce tardive dyskinesia.[59]

The restless legs syndrome is almost certainly the commonest movement disorder in pregnancy, occurring in up to 20% of pregnancies. There is an association with folate deficiency, and if folate concentrations are low

this should be corrected. If further drug treatment is necessary, levodopa/carbidopa in low dose is probably the least teratogenic of the agents reported effective in this condition. Fortunately, it usually remits in the puerperium.

Pregnancy in patients with neurological disease

Common neurological conditions in young women include migraine, other forms of headache, and epilepsy. Less commonly, patients with multiple sclerosis and muscle and neuromuscular junctional disease may require special advice and treatment. The enormous range of neurological diagnoses obviously precludes a detailed consideration of the special problems posed by any but the most common.

MIGRAINE AND OTHER HEADACHES

The commonest causes of troublesome headache in young women are migraine and tension headache. Migraine usually becomes less frequent during pregnancy,[60] but it is such a common condition that there are still many women with bad (and even worsening) migraines during pregnancy. Less commonly, migraine may occur for the first time during pregnancy. The diagnosis is usually straightforward, but it pays to remember that other important causes of headache have a slightly increased incidence in pregnancy, particularly benign intracranial hypertension, tumours (including pituitary adenomas), and cerebral venous thrombosis. When the headaches are bearable, many women prefer to avoid medication altogether during pregnancy.

If simple analgesia is necessary, then paracetamol is preferable to aspirin, which (as an inhibitor of prostaglandin synthesis) may delay the onset of labour, increase intrapartum blood loss, impair neonatal haemostasis, and cause premature closure of the ductus arteriosus.[61] Paracetamol does cross the placenta, but no increase in birth defects has yet been attributed to its use. Non-steroidal anti-inflammatory drugs such as ibuprofen and naproxen are generally safe during the first two trimesters, but carry similar risks to aspirin and because of the risks of premature closure of the ductus, decrease in amniotic fluid volume, and inhibition of labour and bleeding, should be avoided in the third trimester.[62] Metoclopramide has not been reported to cause congenital malformations.[63] Animal studies using sumatriptan have failed to show teratogenic effects in rats or rabbits but even so, use in human pregnancy must still be regarded as experimental. In 159 pregnancy outcomes reported to the manufacturers up to September 1996, 134 were without birth defects. There were six with birth defects (showing no consistent pattern), nine spontaneous pregnancy losses, eight induced abortions, and two stillbirths. Four of the birth defects included came from 150 pregnancies in whom exposure occurred in the first trimester (data from GlaxoWellcome, April 1997).

In patients having frequent and disabling attacks, prophylaxis may be necessary. Beta blockers (atenolol and propranolol) have both been used extensively during pregnancy. There is no evidence of teratogenicity with propranolol, although beta blockers do reduce placental perfusion which may result in intrauterine growth restriction. Despite these caveats, beta blockers are generally considered as appropriate first line prophylactic drugs in the treatment of disabling and frequent migraines during pregnancy.[64] As an alternative, tricyclic antidepressants (such as imipramine and amitriptyline) are useful for prophylaxis of both migraine and tension headache. No significant increases in birth defects have been reported.[65] Infantile tachycardia and urinary retention have rarely been reported and it may be sensible to reduce the dose during the last few weeks of pregnancy.[66] Unlike beta blockers and tricyclic antidepressants (in which most of the prescribing in pregnancy is for indications other than headache), there is little information available on which to base decisions about using pizotifen. Data collected by the manufacturers up to September 1994 include 30 observations on outcome of pregnancy. Eighteen pregnancies resulted in normal babies. Seven had (all different) malformations. Five aborted (four spontaneously). (Data on file, Sandoz Pharmaceuticals.) These few abnormal observations are all retrospective and many more mothers must have taken this drug in the first few weeks of pregnancy even before knowing they were pregnant. Nevertheless, the manufacturers recommend its use in pregnancy only in "compelling circumstances"

MULTIPLE SCLEROSIS

The effect of pregnancy on multiple sclerosis has been a subject of much debate over many years. In a recent Swedish study, the authors reported a significantly reduced incidence of relapses during pregnancy, with no rebound increased risk in the puerperium.[67] Our own interpretation of the literature is that whereas the rate of new relapses falls a little in pregnancy, there is a similar increase in the puerperium. So whereas pregnancy does not cause an overall increase in the risk of relapse, if one is going to occur it is more likely in the puerperium than during the later part of the pregnancy.[68 69] A recent MR study involving two patients showed a decrease in MR disease activity during the second half of pregnancy and then a return to prepregnancy levels in the puerperium.[70] Pregnancy probably has little, if any, effect on longer term disability.[71 72]

EPILEPSY

Maternal epilepsy increases the risk of fetal malformation around two to threefold and it is assumed that much of this increase in risk is due to the drugs taken. The older agents (phenytoin, valproate, and carbamazepine) are all associated with a similar overall risk. In patients on valproate and carbamazepine a higher fraction of this risk is accounted for by an increase in the frequency of spina bifida (about 1% for carbamazepine and 2% for valproate).[73 74] All of the risks are probably increased by polytherapy.[75 76] The risk of spina bifida may be reduced if mothers take folate supplements and our own practice is to

prescribe folate supplements from the time of diagnosis in women of childbearing potential.[77]

The manufacturers of vigabatrin warn against its use in pregnancy because of an increased incidence of cleft palate in rabbits. Lamotrigine and gabapentin have not caused teratogenicity in animals, but the available data in humans are very few. Data on lamotrigine in monotherapy and polytherapy collected by the manufacturers up to September 1996 include 6.5% (four of 62) pregnancy outcomes with birth defects, with no pattern to the defects seen (data from GlaxoWellcome, April 1997). The use of these agents as preferred therapy in pregnancy is thus (at least for the time being) an act of faith. Topiramate has been shown to be teratogenic in animal studies.

There is a grand tradition of monitoring anticonvulsant concentrations during pregnancy and adjusting doses to maintain concentrations in the hope that this will prevent seizures. In favour of the monitoring strategy, it is true that women who have seizures during pregnancy often have low anticonvulsant concentrations. But we also know that compliance is often poor (sometimes patients deliberately reduce or stop their pills, to "protect" their child) and that some tablets are swallowed and vomited back up again. Monitoring concentrations in pregnancy has not been shown to be better than reappraising the need for ongoing medication, counselling about compliance, and adjustments to dosage if necessary on the basis of clinical features. If they are to be monitored, then free drug concentrations should be followed, as bound and free concentrations may change in opposite directions during pregnancy.[78–80]

Generalised tonic-clonic seizures can lead to profound fetal bradycardia.[78 81] Fetal cerebral haemorrhage and death have been reported after a series of seizures during pregnancy.[82] This underscores the need for good seizure control during pregnancy in the interests of fetal wellbeing. Rarely (non-eclamptic) epilepsy occurs only during pregnancy; recurring with successive pregnancies.[83] Status epilepticus is a serious complication of epilepsy and death of the child or mother have both been reported as a consequence. It should be treated along conventional lines.[84]

Mothers taking enzyme inducing drugs should receive orally 20 mg vitamin K_1 daily for a week before delivery. If the exact date of delivery is not known in advance (the usual situation), it seems sensible to start K_1 a month before the expected delivery date.[85] Alternatively, the mother can be given 10 mg K_1 parenterally during labour. Administration of vitamin K_1 to the newborn (which is almost universal practice anyway, to prevent the rare but serious condition of haemolytic disease of the newborn) is recommended in these circumstances.

Whereas most anticonvulsant drugs pass into breast milk, they do so in low concentrations and yield only a tiny fraction of the lowest recommended daily dose for an infant.[86] Breast feeding can therefore be encouraged.

DYSTONIA

We are not aware of any evidence to suggest that dystonia is more common in pregnancy than at other times. Of current interest is the question of whether botulinum toxin injections confer any risk to the foetus. Clinical experience suggests that continued use of this agent is probably safe but until we have more data the safest approach must be to defer further injections during pregnancy.[87]

PARKINSON'S DISEASE

Parkinson's disease is unusual in young women, but can occur and may require special consideration. Levodopa crosses the placenta (as does carbidopa in smaller concentration),[88] but even though published experience with the use of levodopa in pregnancy is limited, its efficacy in treating Parkinson's disease probably outweighs any potential for fetal harm or maternal complications.[59] Bromocriptine has been used more widely in pregnancy (for the treatment of pituitary disease) without problems, but is usually less potent in its antiparkinsonian effect.

PERIPHERAL NERVE DISORDERS

Chronic inflammatory demyelinating polyneuropathy

Women with chronic inflammatory demyelinating polyneuropathy probably have more relapses during pregnancy than at other times.[89] Intravenous immunoglobulin treatment has been used for therapy in non-pregnant women with chronic inflammatory demyelinating polyneuropathy. It has also been used over several years in pregnant women with recurrent fetal loss associated with the antiphospholipid syndrome, without obvious ill effects.[90]

Hereditary sensorimotor neuropathy

Patients with hereditary sensorimotor neuropathy type I have a similar rate of obstetric complications to other pregnant women.[91] Eight of 21 (38%) in one study reported increasing weakness during pregnancy. With childhood onset disease, there is no obvious way of predicting whether deterioration will occur in any person.[91] Deterioration may be severe enough to require artificial ventilation.[92]

MYASTHENIA GRAVIS

Around a third of women with myasthenia gravis deteriorate neurologically during or after pregnancy. Pyridostigmine appears safe, also plasma exchange and steroids (see below). Thymectomy is possible during pregnancy,[93] but probably better performed earlier.

Myasthenia has little effect on pregnancy. The uterus (being smooth muscle) is unaffected, although the striated muscles used during the expulsive phase of labour may be affected and assisted (forceps) delivery may be necessary. Caesarean section is necessary only for obstetric indications. Magnesium sulphate and neuromuscular blocking agents are important members of the "drugs to avoid" list for pregnant myasthenic mothers.

Up to 20% of infants born to mothers with myasthenia will have transient neonatal

myasthenia; symptoms typically start in the first one to four days. Small doses of anticholinesterase drugs are usually needed for a few days.

THE USE OF STEROIDS IN PREGNANCY

Dexamethasone is not known to be linked with congenital defects. Its short term use to stimulate fetal lung maturation in patients with premature labour is not associated with long term fetal harm. Dexamethasone crosses the placenta, however, and infants may have short lived leukocytosis.[94] Prednisolone also seems to have little effect on the developing fetus; there have been little more than anecdotal reports of newborn immunosuppression or fetal deformity and the available evidence supports the use of prednisolone to control various maternal diseases.[95] Because prednisolone is metabolised before crossing the placenta it is preferred to dexamethasone when steroids must be given for more than a few days during pregnancy.[96] High dose steroids in pregnancy may be associated with mineralocorticoid side effects (oedema and rising blood pressure) which may mimic pre-eclampsia.

POSTSCRIPT

Finally, although there are a few reports on delusions of pregnancy in men, this is usually symptomatic of a prior cerebral disorder.[97] Some men experience symptoms such as weight gain, nausea, and toothache during their partner's pregnancies (Couvade syndrome). But most men actually come to medical attention less often when their wives are pregnant than at other times.[98] We are unaware of any study of specific neurological symptoms in the partners of pregnant women.

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