

Medical problems in pregnancy

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ABSTRACT

The prevalence of medical problems in pregnancy is increasing because of a complex interplay between demographic and lifestyle factors, and developments in modern medicine. Maternal mortality and morbidity resulting from treatable medical conditions, such as venous thromboembolism, epilepsy and autoimmune disease, have not decreased in recent years. This is despite a marked decrease in overall maternal mortality. It is vital that all physicians acquire a basic knowledge and understanding of medical problems in pregnancy. This includes prepregnancy measures such as counselling and optimisation of medical therapy, as well as multidisciplinary management throughout pregnancy and the postpartum period. Prompt recognition and treatment of acute and chronic illness is of clear benefit, and most drugs and many radiological investigations may be used in pregnancy.

KEYWORDS: Biologics, maternal mortality, obstetric medicine, pregnancy

Introduction

The prevalence of medical problems in pregnancy is increasing because of a complex interplay between demographic and lifestyle factors, and developments in modern medicine. Women are delaying childbearing until later in life. Older women are more likely to have acquired medical disorders, such as hypertension and obesity; they are also at higher risk of gestational diabetes and venous thromboembolism. Medical and surgical advances have enabled women to become pregnant despite having chronic conditions that would previously have precluded pregnancy. However, this is not without risk – the MBRRACE (Confidential Enquiries into Maternal Deaths and Morbidity) report¹ revealed that two-thirds of maternal deaths in 2011–13 were in women with known medical comorbidities and 30% of mothers that died were obese (Fig 1). Additionally, for every maternal death, there are many others that suffer severe morbidity during or soon after pregnancy. Data from the

Intensive Care National Audit and Research Centre (ICNARC) show that the admission rate to critical care during the period 2009–12 was 290 per 100,000 maternities, compared to a maternal mortality rate of less than 11 per 100,000 over the same period.¹

Maternal deaths can be classified as direct ('obstetric') or indirect ('medical') (Box 1). As Fig 2 illustrates, there has been a worrying increase in the rate of indirect deaths over the last 25 years and while this has plateaued, direct death rates continue to fall. Medical conditions now dominate the list of leading causes of maternal death (Fig 3). Therefore, it is vital that all physicians acquire a basic knowledge and understanding of medical problems in pregnancy.

The approach to managing medical problems in pregnancy is summarised in Fig 4. The process should begin before conception, and all physicians should consider delivering prepregnancy counselling as part of their routine inpatient or outpatient consultations with women of reproductive age. The MBRRACE reports call for action to 'ensure that physicians are appropriately trained in... the care of pregnant women, and that services are designed for women with medical conditions... including pre-pregnancy, during pregnancy and delivery, and postpartum'. This is clearly a very broad subject, and this article aims to provide a snapshot. We discuss a few of the important causes of maternal mortality, as well as some common medical causes of morbidity that present particular diagnostic and therapeutic challenges in pregnancy.

Box 1. Definitions of maternal deaths (World Health Organization 2010).

Maternal death: Death of a woman while pregnant or within 42 days of the end of the pregnancy (the puerperium) from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

Direct: Deaths resulting from obstetric complications of the pregnant state (pregnancy, labour and puerperium), from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above. Examples include genital tract sepsis, hypertensive disorders of pregnancy and thrombosis.

Indirect: Deaths resulting from previous existing disease, or disease that developed during pregnancy and which was not the result of direct obstetric causes, but which was aggravated by the physiological effects of pregnancy. Examples include cardiovascular disease, neurological disorders, non-genital infections and psychiatric causes.

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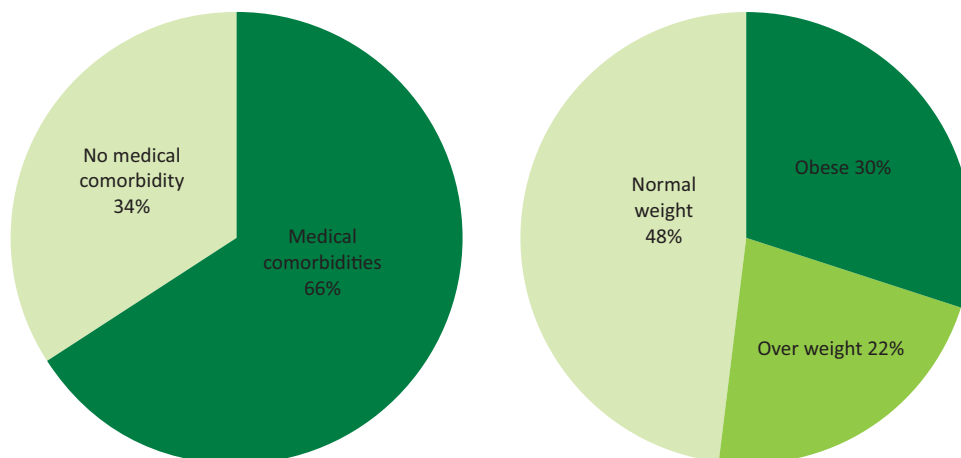


Fig 1. Selected characteristics of the mothers who died in 2011-13. Adapted from the 2015 MBRRACE report.¹

Venous thromboembolism

Venous thromboembolism (VTE) is the leading direct cause of maternal death in the UK and the trend of falling mortality rates from 2002 to 2008 has reversed in recent years.

The relative risk of VTE in pregnancy is increased four- to sixfold compared with the general population. This risk increases with gestational age, reaching a maximum just after delivery. Caesarean section further increases this risk, particularly if this is performed as an emergency.¹ Certain women are, because of medical or obstetric factors, at particularly high risk and therefore require antenatal and/or postpartum thromboprophylaxis with low molecular weight heparin (LMWH). LMWH is safe and effective in pregnancy and recent guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) provide a detailed approach to risk stratification.²

As well as preventative measures, it is also important to promptly recognise and treat acute VTE in pregnancy. Venous stasis is more marked in the left leg because of compression of

the left iliac vein by the right iliac artery and ovarian artery. 85% of deep vein thrombosis in pregnancy are on the left side and 70% are ilio-femoral (which are more prone to lead to pulmonary embolism).³

A thorough history and examination is important when assessing for acute pulmonary embolism (PE) because the differential diagnosis includes cardiac disease and aortic dissection. A chest X-ray (CXR) should always be performed first (negligible radiation risk) as pneumonia and pneumothorax can present similarly. If PE is still suspected, then a nuclear medicine perfusion (VQ) scan or computerised tomography pulmonary angiogram (CTPA) should be performed. Investigation should not be withheld simply because the patient is pregnant. The maternal and perinatal risks of missing a diagnosis of VTE are thought to be greater than the risks associated with the investigations; the risks to the fetus are small with either imaging modality. Compared with CTPA, VQ may carry a very slightly increased risk of childhood cancer (1/280,000 versus less than 1/1,000,000).⁴ However, CTPA is associated with a

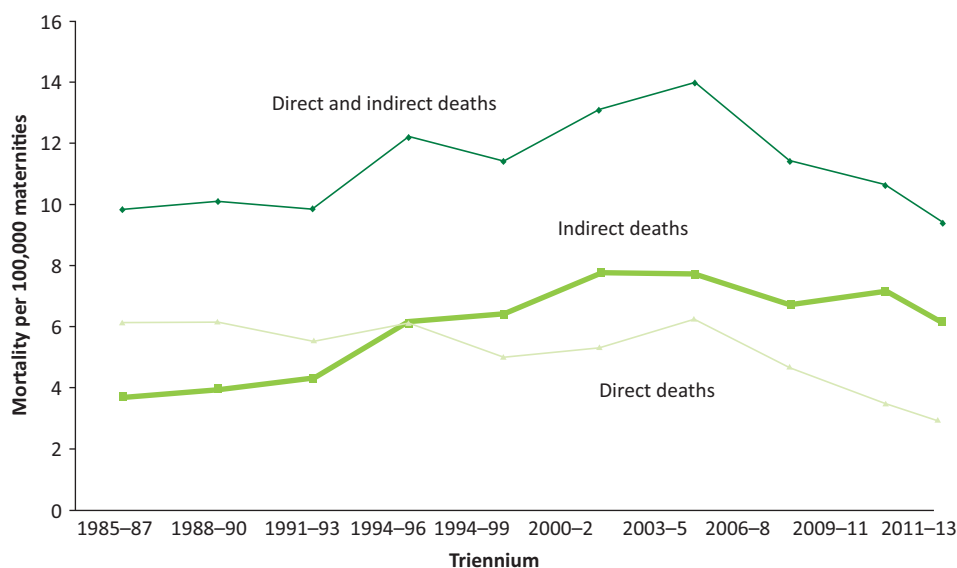


Fig 2. Direct and indirect maternal mortality rates per 100,000 maternities in the UK, 1985-2013 (preliminary data 2011-13). Deaths from indirect causes have risen and plateaued in recent years. In contrast, deaths from direct causes are falling. Adapted from the 2015 MBRRACE report.¹

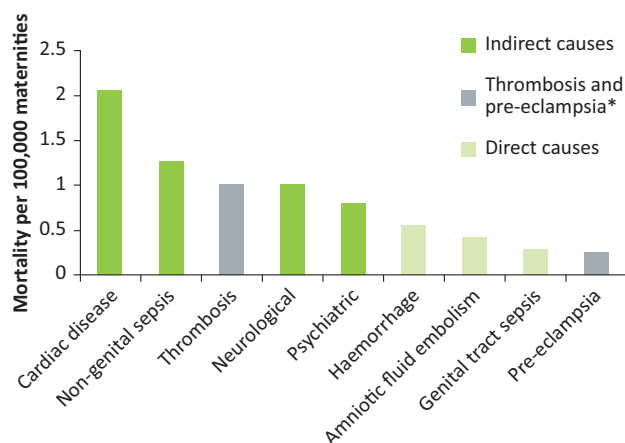


Fig 3. Direct and indirect causes of maternal mortality per 100,000 maternities in the UK, 2011–13. Adapted from the 2015 MBRRACE report.¹ *Although thrombosis and pre-eclampsia are classified as ‘direct’, they are often associated with medical risk factors and/or comorbidities.

significantly higher risk of maternal breast cancer (lifetime risk increased by up to 13.6%; background risk of 1/200).⁵

Pre-test probability assessment (eg Wells Score) is not validated in pregnancy and D-dimer testing is not recommended outside the research setting.

Treatment dose LMWH should be commenced immediately and continued if the diagnosis is confirmed. The doses required are higher than in non-pregnant patients and are listed in the RCOG guidelines.⁶ Warfarin should be avoided in pregnancy, as should direct oral anticoagulants such as rivaroxaban. However, pregnancy is not a contraindication to thrombolysis, which can be considered in massive life-threatening PE.

Epilepsy

Epilepsy affects 1% of the UK population and 23% of people with the condition are women of childbearing age.⁷ There are two main aspects to the management of epilepsy in pregnancy. Firstly, there is the impact of epilepsy on pregnancy outcomes (and vice-versa); secondly, there are the implications of fetal anti-epileptic drug (AED) exposure.

It is essential that epilepsy is recognised as a high-risk condition. Maternal mortality is tenfold higher in patients with epilepsy than in those without the disorder⁸ and more women

now die from epilepsy in pregnancy than from pre-eclampsia and eclampsia. Epilepsy is also associated with an increased risk of obstetric haemorrhage, hypertensive disorders of pregnancy and fetal growth restriction.⁹

The 2014 MBRRACE report⁶ highlighted that the majority of women who died from epilepsy-related causes had poorly controlled epilepsy pre-pregnancy and very few had received pre-pregnancy counselling. This emphasises the need to initiate the process before conception. Because a significant proportion of pregnancies are unplanned, it should be assumed that all women of childbearing age with a diagnosis of epilepsy may become pregnant at some stage in their life. This should prompt opportunistic pre-pregnancy counselling at the time of diagnosis or initiation of drug treatment and at subsequent contacts with healthcare professionals.

Most women with epilepsy will not experience a change in seizure frequency during pregnancy and women who have been seizure-free for several years are unlikely to have seizures in pregnancy.³ Those with poorly controlled epilepsy are at the highest risk of deterioration, injury and death due to SUDEP (sudden unexpected death in epilepsy). However, even in those with well-controlled disease, deterioration may occur following discontinuation of anti-epileptic medications, or if there is a significant fall in drug levels. This may occur because of poor compliance, nausea and vomiting, and altered pharmacokinetics. Pregnancy results in an increased volume of distribution and increased hepatic and renal clearance of many drugs. Lamotrigine, in particular, may require significant dose increases in pregnancy. The results of a large multicentre study (EMPIRE) may clarify the role of therapeutic drug monitoring.

All AEDs are teratogenic (Table 1) but the risks of uncontrolled epilepsy almost always outweigh the risks to the fetus posed by these medications. Sodium valproate carries the highest risk of malformations and is also associated with impaired childhood psychomotor development. It is usually switched to an alternative drug pre-conception. Women of childbearing age should only be commenced on sodium valproate if there is no other suitable treatment option. Other anti-epileptics are usually continued through pregnancy although careful counselling is required to ensure that the patient understands the benefits and risks.

Headache

Headache is a common complaint in the general population; patients presenting to the emergency department with headache are disproportionately female (71%) and between 18 and 49 years of age (71%).¹⁰ Therefore, it is unsurprising that it is a relatively frequent presentation in pregnant women. The vast majority of headaches are self-limiting and benign in aetiology but there are some potentially serious causes to be considered. Certain causes of headache warrant a particularly high index of suspicion in pregnant patients.

It is vital to take a thorough history from any patient presenting with headache. Physical examination is often unremarkable and a good history can, in most cases, provide the information required to formulate a working diagnosis.

Primary headaches, such as migraine and tension headache, account for most headaches in pregnancy. The majority of women with pre-existing migraine notice a reduction in frequency and severity of attacks, possibly due to a reduction

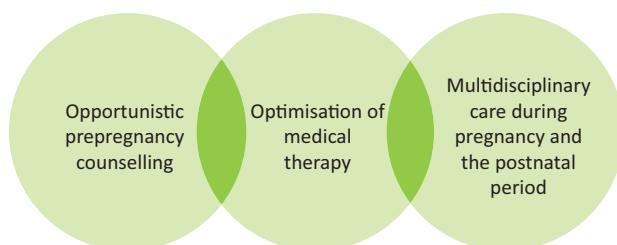


Fig 4. The three aspects of managing women with medical problems in pregnancy.

Table 1. Anti-epileptic drugs (AEDs) in pregnancy

Drug	Pharmacokinetic considerations in pregnancy	Teratogenic effects
Sodium valproate		High risk (4.7–13.8%) of major fetal malformations (neural tube defects, congenital heart defects) High rate (30–40%) of impaired psychomotor development and reduced IQ in the child; risk of childhood autism increased fivefold The risks are dose-dependent and increase when valproate is combined with other AEDs
Phenytoin	Highly protein-bound; dose increases rarely required	Increased risk of congenital heart defects Alternative drugs should be used where possible
Lamotrigine	Dose may need to be increased two- to threefold	Associated with fetal malformations, but risk appears relatively low. If epilepsy is well controlled on these drugs then they should be continued
Carbamazepine, levetiracetam	Drug levels and dose adjustment recommended only if there is a change in seizure frequency	
Benzodiazepines (diazepam, lorazepam, clobazam)		Not teratogenic in monotherapy, but in most circumstances used as add-on therapy with another AED

in reproductive hormonal fluctuation. However, around 10% experience a worsening of symptoms and migraine may present *de novo* in pregnancy.¹¹

If clinical assessment supports a diagnosis of migraine or tension headache, then no further investigations are required. Lifestyle measures and simple analgesia are the first-line treatments. Patients should be advised to get adequate sleep and to avoid dietary triggers and dehydration. Paracetamol is acceptable for use in pregnancy and ibuprofen can be prescribed for short-term use in the first and second trimesters. Opiates are not harmful to the fetus but should be used sparingly because of their side-effect profile and tendency to cause rebound headaches. Metoclopramide, cyclizine or prochlorperazine can be added to treat nausea and vomiting.

There are increasing safety data on triptans to treat migraine in pregnancy.^{12,13} Sumatriptan exposure has not been associated with fetal malformations or adverse outcomes and, if other treatments have failed, it may be used to treat acute migraine attacks.

If attacks are frequent, then prophylactic medication should be considered. Low-dose aspirin is the first-line agent. β -blockers (eg propranolol) can be added and, if this is not effective, then a tricyclic antidepressant (eg amitriptylline) can be used as a third-line option.

It is important to consider secondary causes in the differential diagnosis of headache, which may require urgent investigation. Pre-eclampsia may present with headache and meningitis presents as headache with fever and neck stiffness. Pregnancy significantly increases the risk of subarachnoid haemorrhage and cerebral venous thrombosis. The risk is highest in the puerperium (first 6 weeks post-delivery).

Urgent imaging should be performed in patients who present with severe thunderclap headache, features of raised intracranial pressure, neurological deficits or seizures. CT brain is safe in pregnancy, readily available and indeed superior to MRI in detecting acute haemorrhage. The radiation dose is

small and the fetal exposure is negligible. However, magnetic resonance venogram is the preferred imaging modality to detect cerebral venous thrombosis.

Reversible cerebral vasoconstriction syndrome is a recently recognised disorder of cerebrovascular tone, which can cause severe sudden onset headache and atypical subarachnoid haemorrhage in the postpartum period.¹⁴ It may be associated with hypertension. Diagnosis is on MRI angiography (with a characteristic appearance of vascular beading) and treatment is with nimodipine. It usually resolves within 3 months.

Inflammatory and autoimmune conditions

Systemic inflammatory diseases, such as systemic lupus erythematosus, rheumatoid arthritis and inflammatory bowel disease, are relatively common in women of childbearing age. The approach shown in Fig 4 is particularly relevant for women with these conditions.

Good disease control is of obvious benefit to the mother but it also reduces adverse fetal and neonatal outcomes as well as improving fertility.¹⁵ A 2013 meta-analysis showed that women who conceive with active inflammatory bowel disease have a higher rate of active disease during pregnancy (46–55%) than those who conceive while in remission (23–29%).¹⁶ Similarly, systemic lupus erythematosus flares during pregnancy are more common in those with active disease at conception.¹⁷

A major source of uncertainty for patients and healthcare professionals relates to the safe use of medications during pregnancy. Very few drugs are licensed for use in pregnancy, so safety information is often derived from animal studies, case series, registry data and extrapolation from non-pregnant subjects. The US Food and Drug Administration recently discontinued the traditional pregnancy categories A, B, C, D and X as they were often misinterpreted and misused. There is growing evidence of drug safety in pregnancy and it is vital to avoid cessation of important medications because of theoretical

or unwarranted concerns. It is also important to note that there is a background incidence of major congenital malformations (2–3%), miscarriage (10–20%) and stillbirths (0.5%).¹⁸ This is irrespective of any drug exposure. This section aims to provide an update on the pharmacological treatment of inflammatory disorders in pregnancy.

Corticosteroids

Prednisolone and methylprednisolone are extensively metabolised by the placenta and less than 10% reaches the fetus. Several large studies have not found any significant adverse effect (major malformations, prematurity, low birthweight) attributable to these drugs¹⁹ although there is an increased maternal risk of gestational hypertension and diabetes. Prednisolone should be used in preference to fluorinated steroids, such as dexamethasone, as the latter cross the placenta to a greater degree.

Corticosteroids play a key role in the treatment of disease flares in patients with rheumatological conditions or inflammatory bowel disease as well as acute asthma. They should be used at any stage of pregnancy if clinically indicated.

There is evidence that physicians under prescribe systemic steroids when managing pregnant patients with asthma, resulting in worse outcomes for these women;²⁰ it is important to avoid this error when managing pregnant patients with any condition requiring steroid treatment.

Immunomodulators and immunosuppressants

Many of the drugs used in autoimmune, rheumatological and inflammatory bowel disease can be used in pregnancy. Table 2 shows a summary for commonly used drugs and counselling about pregnancy should be undertaken when these drugs are initiated. There are good safety data for hydroxychloroquine, sulfasalazine, mesalazine and azathioprine, none of which are associated with any increase in congenital malformation rates or pregnancy loss. Although azathioprine was, in one study,²¹ associated with neonatal anaemia, this was a small uncontrolled study and the results were not significant after adjustment for

gestational age.²² A prospective study is currently underway to further evaluate this.

The calcineurin inhibitors ciclosporin and tacrolimus are also safe for use in pregnancy. However, drug levels should be monitored closely as drug metabolism and clearance may vary during and after pregnancy. Maternal blood pressure, blood glucose and renal function should also be checked regularly.

The drugs that should be avoided in pregnancy are methotrexate, mycophenolate mofetil, leflunomide and cyclophosphamide. Adequate contraception is imperative. These drugs should be stopped prior to conception and changed to an alternative medication. It is important to address this in pre-pregnancy counselling and to aim for optimal disease control on the new drug prior to conception. In exceptional circumstances, cyclophosphamide may be used in the second and third trimesters for conditions such as breast cancer and rapidly progressive interstitial lung disease.²³

Biologics

‘Biologic’ anti-TNF α drugs, such as infliximab, adalimumab and etanercept, have revolutionised the treatment of systemic inflammatory disorders. All three can be safely used in early pregnancy; they do not cross the placenta until after 16 weeks of gestation. There are no significant associations with a particular pattern of congenital malformations or adverse pregnancy outcomes. Beyond 16 weeks, decisions about continuation are individualised based on the drug clearance rate, degree of placental transfer and the patient’s clinical condition.

Infliximab and adalimumab are immunoglobulin G antibodies and are therefore actively transported across the placenta from 16 weeks, resulting in higher drug levels in the neonate than in the mother. Etanercept appears to have a lower rate of placental transfer.

To minimise neonatal levels at birth, these drugs should be discontinued, if possible, by 20 weeks for infliximab and 28 weeks for adalimumab or etanercept. However, in some patients with active inflammatory disease, it is acceptable and indeed necessary to continue treatment throughout pregnancy. The British Society of Rheumatologists and European League Against Rheumatism have recently issued detailed guidance^{24,25} on this topic.

If infliximab is used throughout pregnancy, it can take up to 7 months for blood levels to become undetectable in the infant. Adalimumab has a slightly shorter duration of action and takes up to 11 weeks to become undetectable. The effect on the neonate is unclear and there are theoretical concerns about neonatal immunosuppression. However, data from the PIANO registry²⁶ are reassuring: third trimester anti-TNF α use had no effect on infant growth, development and immune development in the first year of life and a systematic review²⁷ found no increased risk of infections up to 1 year of age. There has been a single isolated case of fatal disseminated *Bacillus Calmett-Guerin* (BCG) in an infliximab-exposed infant who received the vaccine at 3 months of age. It is therefore recommended that infants exposed to anti-TNF α drugs should not receive live vaccines in the first 6 months of life. All of these drugs may be detectable in breast milk at very low levels, but they are very poorly absorbed via the oral route so breastfeeding is considered safe.

Table 2. Immunosuppressants in pregnancy

Acceptable at all stages of pregnancy	Acceptable in early pregnancy (but can be continued if required for disease control)	Avoid in all stages of pregnancy
Prednisolone	Infliximab – stop at 20 weeks if possible	Methotrexate
Ciclosporin	Adalimumab – stop at 28 weeks if possible	Leflunomide
Tacrolimus		Mycophenolate
Hydroxychloroquine	Etanercept – stop at 28 weeks if possible	Cyclophosphamide
Sulfasalazine		
Mesalazine		
Azathioprine		

Table 3. Antihypertensive drugs in pregnancy

1st choice	Alternative first-line	Second-line	Third-line	Contraindicated in pregnancy
Labetalol	Nifedipine (MR)	Methyldopa	Doxazosin	ACE inhibitors (safe when breastfeeding*)
		Amlodipine	Hydralazine	Angiotensin II receptor antagonists Spironolactone
			Selective β -blockers	

*Avoid in acute kidney injury. Enalapril and captopril are the preferred agents, as safety data are limited for other drugs in this class.
ACE = angiotensin-converting enzyme; MR = modified release

There are a number of newer anti-TNF α drugs, some of which have been modified to alter the pharmacokinetic profile. Certolizumab pegol is an antigen-binding fragment of a monoclonal anti-TNF α antibody (lacking the Fc region) that has been conjugated with poly-ethylene glycol. It has low rates of placental transfer and early data suggest that it is compatible with all three trimesters of pregnancy.

Hypertensive disorders of pregnancy

Hypertension is the most common medical problem in pregnancy. In normal pregnancy, blood pressure falls by around 10 mmHg in the first half of pregnancy, and then gradually returns to prepregnancy levels by term. Hypertension in pregnancy increases the risk of pre-eclampsia, preterm delivery, fetal growth restriction, placental abruption and perinatal death. Women may have pre-existing hypertension or gestational hypertension (developing after 20 weeks of gestation). Pre-eclampsia is a disease specific to pregnancy and can be defined as new/worsening hypertension with significant proteinuria or organ dysfunction (Fig 5).²⁸ Pre-eclampsia often occurs *de novo*, but women with pre-existing hypertension may develop superimposed pre-eclampsia, and gestational hypertension may also evolve into pre-eclampsia. It requires hospital admission for close monitoring and the only cure is delivery, which may be required urgently in severe cases. Pre-eclampsia is associated with a doubling of the lifetime risk of developing hypertension,

coronary artery disease, cerebrovascular disease and chronic kidney disease. In women with early-onset pre-eclampsia (before 34 weeks), the risk is increased up to eightfold. Therefore, a pregnancy history should be taken when assessing cardiovascular risk in women.

It is common practice to aim for target blood pressure lower than 150/100 mmHg in pregnancy and this is consistent with the 2010 National Institute for Health and Care Excellence guidelines.²⁹ There were theoretical concerns that lower targets might compromise uteroplacental circulation. However, recent evidence from the CHIPS trial³⁰ showed that neonatal outcomes are no different with a target diastolic blood pressure of 81–85 mmHg compared with 100–104 mmHg and severe maternal hypertension was more frequent in the less tight control (100–104 mmHg) group. Therefore, when treating hypertension in pregnancy, the aim should now be tight control, with a target diastolic blood pressure of 81–85 mmHg.

If pharmacological treatment is required, labetalol (non-selective α - and β -blocker) or modified-release nifedipine (calcium channel blocker) are the first-line drugs in pregnancy (Table 3). Methyldopa and amlodipine are second-line options.

Importantly, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and spironolactone are contraindicated in pregnancy and should be switched (ideally pre-conception) to an alternative agent. However, angiotensin-converting enzyme inhibitors can be reintroduced postpartum and are safe when breastfeeding.³¹

Conclusions

Maternal mortality and morbidity resulting from treatable medical conditions have not decreased in recent years, despite a marked decrease in overall maternal mortality. Part of the solution is to improve the training of physicians in the management of pregnant patients, including pre-conception counselling. Prompt recognition of acute illness and optimal treatment of chronic conditions is of clear benefit, and most drugs and many radiological investigations can be used in pregnancy. ■

Conflicts of interests

The authors have no conflicts of interests to declare.

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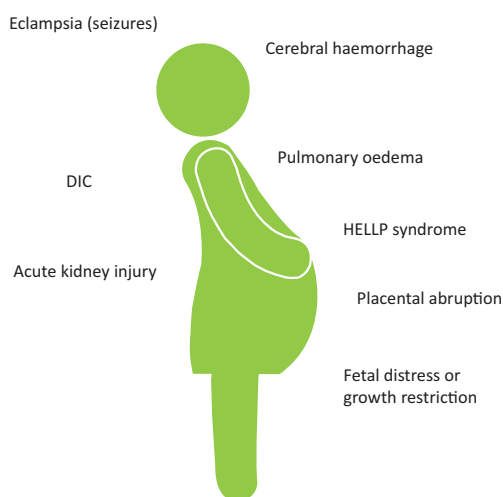


Fig 5. Major complications of pre-eclampsia. DIC = disseminated intravascular coagulation; HELLP = haemolysis elevated liver enzymes low platelets

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