Seminar

Pre-eclampsia

James J Walker

Pre-eclampsia is associated with significant morbidity and mortality for mother and baby, but it resolves completely post partum. Despite a steady reduction in maternal mortality from the disorder in more developed countries, it remains one of the most common reasons for a woman to die during pregnancy. The disorder starts with a placental trigger followed by a maternal systemic response. Because both this systemic response and the woman's reaction to it are inconsistent, the clinical presentation varies in time and substance, with many different organ systems affected. With the increasing understanding of the disease process, there have been advances in management, such as antihypertensive therapy, magnesium sulphate, and fluid restriction.

In the UK, the number of maternal deaths from hypertension in pregnancy has fallen steadily over the past few decades (figure 1)[1] as has the complication rate.[2] However, in other parts of the world, the rates of mortality and morbidity remain high[3] and will continue to be so until there are general improvements in maternity services. Trials on prevention have been disappointing,[4] so the mainstays of management of hypertension in pregnancy are integrated antenatal care, access to monitoring services, stabilisation of the maternal condition, and delivery of the baby on the best day in the best way to benefit both mother and child. Antenatal care must provide easy access to monitoring services.[5]

Epidemiology

The epidemiology of pre-eclampsia is complicated by differences in definitions and inaccuracy of diagnosis. A single blood-pressure reading of 140/90 mm Hg or above is not uncommon in pregnancy and was reported in nearly 40% of pregnant women in one study.[6] Such a finding carries little risk to the mother or fetus. Persistent hypertension is diagnosed if a high reading is found on two occasions at least 4 h apart. Persistent hypertension occurs in around 12–22% of pregnancies,[7–9] depending on the populations and definitions used. The type of hypertension can be further defined on the basis of other clinical signs, particularly proteinuria and abnormalities of coagulation.[10]

Hypertension in pregnancy can be classified into two main groups (panel 1): women who are hypertensive when they become pregnant[11] and those who become hypertensive for the first time in the second half of pregnancy.[9] Blood pressure generally falls in the first and second trimesters; therefore women with high blood pressure before the 20th week of gestation are assumed to have pre-existing hypertension.

Although these definitions are important for research and epidemiological purposes, they are less important clinically. All women with raised blood pressure must be carefully monitored for the associated features of pre-eclampsia. Although well-controlled essential hypertension is benign, the frequency of superimposed pre-eclampsia is between 15% and 25%, increasing the maternal and fetal risk.[12,13]

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Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds LS9 7TF, UK (Prof J J Walker FRCOG)
(e-mail: j.j.walker@leeds.ac.uk)

Pre-eclampsia is twice as common in primigravid women as in women having second or later pregnancies.[14] However, with a change of partner, the risk in a multiparous woman increases; this effect suggests that primipaternity is important. Particular men seem to have an increased risk of fathering a pre-eclamptic pregnancy.[15] Women who become pregnant with donor eggs have a higher frequency of pre-eclampsia than women pregnant with their own eggs;[16] this finding suggests that any new fetal factors are important, not necessarily those of paternal origin.

Pathophysiology

Pre-eclampsia is the result of an initial placental trigger, which has no adverse effect on the mother, and a maternal systemic reaction that produces the clinical signs and symptoms of the disorder.[17]

Placental trigger

Pre-eclampsia occurs only in the presence of a placenta. Although it is associated with a failure of the normal invasion of trophoblast cells, leading to maladaptation of maternal spiral arterioles,[18] it can also be associated with hyperplacentation disorders such as diabetes, hydatidiform mole, and multiple pregnancy. The maternal arterioles are the source of blood supply to the fetus (figure 2), and maladaptation of these vessels can interfere with normal villous development. In some cases, compensation can occur, but, in others, poor villous development results in placental insufficiency.[19] Secondary damage, such as fibrin deposition and thrombosis, can then occur within the placenta. These features are found in cases of placental insufficiency, whether pre-eclampsia is present or not.[20] Not all women with the potential placental trigger develop pre-eclampsia, therefore the maternal response must be the decisive factor in development of systemic disease.

Maternal response

Although pre-eclampsia is said to be a vascular endothelial disorder,[21] it is a multisystem disorder with various forms. This variation could be due to different vascular beds being affected to varying degrees, but later research has shown that there is a strong maternal inflammatory response.[17] Although this response has been described in the placental bed,[22] there is far broader immunological systemic activity.[17] These changes may explain many of the clinical signs, including the endothelial-cell dysfunction.

Because pre-eclampsia is diagnosed by the presence of hypertension and proteinuria, the rest of the systemic features can vary from mild cases with little systemic

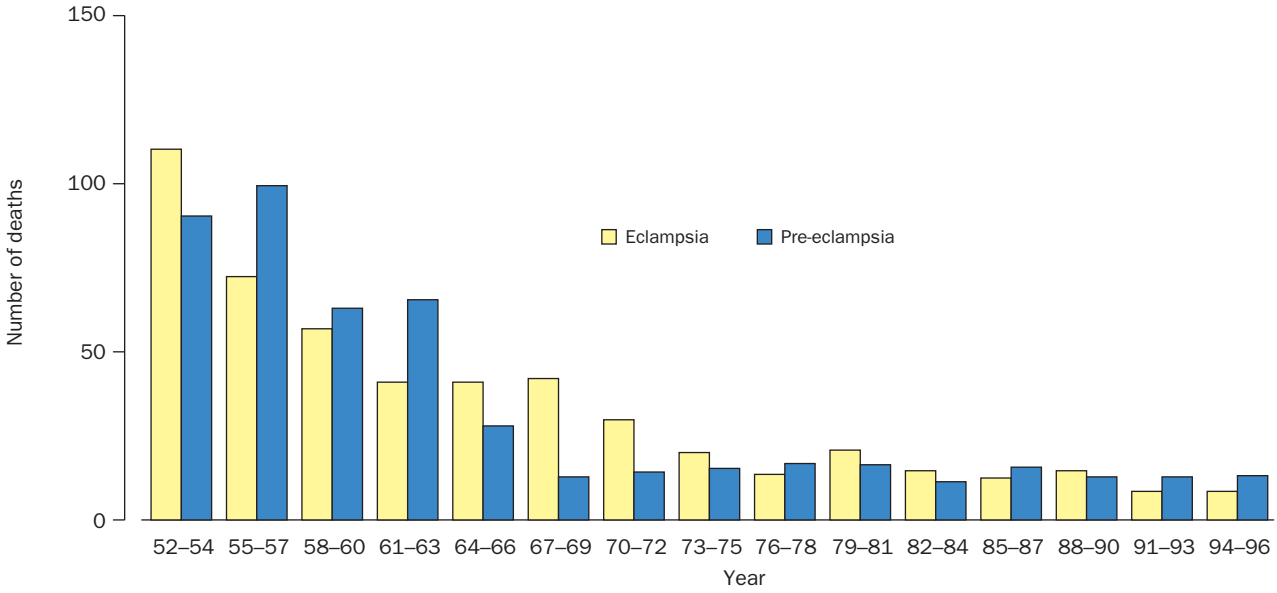

Figure 1: **Maternal mortality associated with pre-eclampsia and eclampsia**

involvement, to multiorgan failure. How extensively the disease develops depends on various modifying factors, which could be genetic or environmental in origin.

Hereditary factors

Pre-eclampsia can be familial,[23] but various groups have studied the genetic basis of this disorder and no persistent results have been obtained with obvious population differences. A single pre-eclampsia gene is unlikely; there are probably several modifier genes along with environmental factors.[24] There have been conflicting results for the genes that encode angiotensinogen, superoxide dismutase, tumour necrosis factor α, methylene-tetrahydrofolate reductase, factor V Leiden, and endothelial nitric oxide synthase. These studies concentrated on maternal genetics and ignored the potential paternal and fetal influences.[15] The results of large multicentre studies with the use of modern chip technology for genome scanning with multiple microsatellite markers are awaited to clarify the role of genetics in the pathophysiology of pre-eclampsia.[24]

Panel 1: **Classification of hypertension in pregnancy**

Pre-existing hypertension (3–5% of pregnancies)[11]
Hypertension before pregnancy or found earlier than 20 weeks of gestation or persisting after the pregnancy ends. Most such patients have essential hypertension but some have renal disease and other medical disorders.

Pregnancy-associated hypertension (12% of pregnancies)[9]
Hypertension occurring de novo after the 20th week of pregnancy and settling within 6 weeks of delivery. This category is divided into two groups.

Gestational hypertension (6–7%)—Hypertension alone with no associated features.

Pre-eclampsia (5–6%)—Hypertension with proteinuria of at least 0·3 g in 24 h (24 h urine collection or protein/creatinine ratio).

Superimposed pre-eclampsia (25% of women with pre-existing hypertension)[12,13]
Signs and symptoms of pre-eclampsia in woman with pre-existing hypertension.

Eclampsia
Convulsions in any woman who has, or then presents with, hypertension in pregnancy of any cause.

Diagnosis and assessment

Hypertension is the most common diagnostic sign, although some women present with convulsions, abdominal pain, or general malaise. Because there are no specific diagnostic investigations, the initial diagnosis of pre-eclampsia remains clinical. The classification of severity is mainly based on the blood-pressure value and the presence of proteinuria; further characterisation is based on the other accompanying signs.[25]

Measurement of blood pressure

There has been much controversy about the method of measuring blood pressure in pregnancy. In the UK, Korotkoff phase IV is generally used, but in other parts of the world, clinicians use Korotkoff phase V. A study by Brown and colleagues suggested that Korotkoff phase V is preferable.[26] What is important is that the method used is consistent and documented. For measurement of blood pressure, the woman should be rested and reclining at an angle of 45°. The blood-pressure cuff should be of appropriate size and placed at the level of the heart. Because of the normal blood-pressure variation, several readings should be used to confirm the diagnosis.

In normal pregnancy, there are substantial cardiovascular changes with a 50% increase in cardiac output and blood volume, which is accompanied by a fall in blood pressure due to peripheral vasodilation. The changes in pre-eclampsia tend to be the reverse. Severe disease is generally associated with a low cardiac output and a high peripheral resistance. However, Bosio and colleagues[27] found both high-output and low-output states and peripheral resistance within a range from normal to high among women with hypertensive disorders of pregnancy. More importantly, serial studies have shown a cross-over effect from high output plus low resistance to low output plus high resistance as the disease progresses.[27]

In pre-eclampsia, the urine protein excretion rises above a threshold of 0·3 g per 24 h. This finding is generally associated with the classic pathological finding of glomeruloendotheliosis,[28] which is not permanent but recovers after delivery. The presence of proteinuria confirms the diagnosis of pre-eclampsia and the concomitant increase in risk for both mother and fetus.[29] The risk is related simply to the presence of proteinuria; it

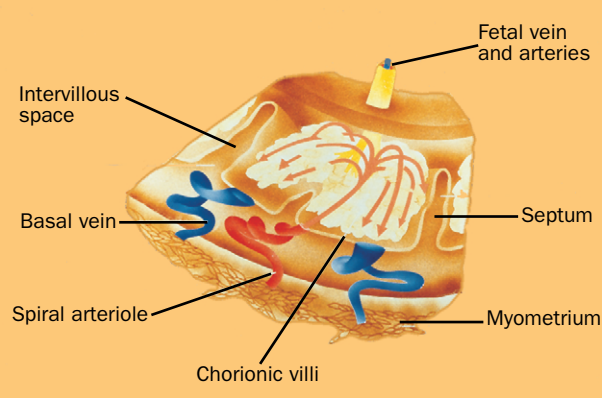

Figure 2: **Diagram of maternal/placental interface showing spiral-artery blood flow and villous structure**

is not affected by the absolute value of or the increase in urinary protein excretion.[30]

Blood pressure and proteinuria can be readily assessed in the antenatal-care setting. If abnormalities are found, the woman should be admitted to hospital or referred to an antenatal day unit for further investigations.[5]

The loss of serum protein and the increase in capillary endothelial permeability lead to a decrease in intravascular volume and increased tissue oedema.[31] All organs can be affected, including the liver (producing abdominal pain), brain (producing headache and convulsion), and the lungs (producing breathlessness). Peripheral oedema also occurs, but it is variable and is not a useful diagnostic sign. The decrease in blood volume can lead to an increase in maternal haemoglobin concentration and is associated with an increased risk of intrauterine growth restriction.[29]

In normal pregnancy, the platelet count can fall below 200×10^9/L because of the normal maternal blood-volume expansion. In pre-eclampsia, the platelet count falls further and is associated with progressive disease.[29] This fall is probably a result of both increased consumption and intravascular destruction. Associated coagulation abnormalities are unlikely if the count is above 100×10^9/L.[32] A low platelet count is one component of the HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets), which carries a particular risk to the mother.[33]

Serum concentrations of uric acid fall in normal pregnancy because renal excretion increases. In pre-eclampsia, there can be a rise in uric acid concentrations that correlates with poorer outcome for both mother and baby.[33] This rise is due mostly to a decrease in renal excretion, but there is probably also increased production secondary to tissue ischaemia and oxidative stress. This variable is a particularly sensitive marker of disease progression and risk.

Liver involvement in pre-eclampsia is very varied but is the cause of the upper epigastric pain commonly seen in the disorder. The liver swells as a result of local oedema secondary to inflammatory infiltrates and obstructed blood flow in the sinusoids. Haemorrhage can occur beneath the liver capsule and may be so extensive as to cause rupture of the capsule into the peritoneal cavity. If a haematoma or haemorrhage is suspected, the liver should be examined by ultrasonography.[34] Liver involvement can be assessed by measurement of alanine aminotransferase and aspartate aminotransferase activities in serum; they increase in pre-eclampsia as a result of leakage across cell membranes. Rises in these enzymes are part of the HELLP syndrome.[33] With substantial liver involvement there are coagulation abnormalities that result from hepatic dysfunction and not disseminated intravascular coagulation, which is a rare complication of pre-eclampsia in the absence of placental abruption.[35]

Renal function is generally maintained in pre-eclampsia until the late stage. In normal pregnancy, there is an increase in creatinine clearance with a concomitant decrease in serum creatinine and urea concentrations. If creatinine concentrations are high early in the disease process, underlying renal disease should be suspected. In severe disease, rises in serum creatinine can be seen and are associated with worsening outcome.[25] Acute renal failure is now rare in pre-eclampsia in more developed countries;[1,36] most cases are associated with haemorrhage or sepsis. Most cases of renal failure are due to acute tubular necrosis, and most patients recover with no long-term renal impairment.[36] Acute cortical necrosis, a permanent cause of renal failure, occurs in less than 4% of all cases of renal failure in pre-eclampsia.[37]

Numbers of neurological sequelae, such as eclampsia and stroke, are decreasing,[2] perhaps because of earlier intervention and delivery or environmental factors. The fall in incidence antedates the use of antihypertensive drugs and magnesium sulphate.[2] Cerebral oedema is associated with convulsions and can be seen on computed tomography and magnetic resonance imaging. This disorder has been described as posterior

Panel 2: **Stepwise management of pregnancy hypertension**

Screening
Screening of women for the risk or signs of hypertension at the antenatal clinic.
Regular blood-pressure checks and analysis of urine.
Referral of those at risk for monitoring in antenatal day unit.

Maternal assessment[5]
Repeated blood-pressure measurement.
Quantitative measurement of protein in urine.
Platelet count, serum uric acid concentration, and tests of liver function (alanine and aspartate aminiotransferase activities).

Antihypertensive therapy[11,46]
Definitely treat if blood pressure is above 170/110 mm Hg.
Consider treatment if blood pressure above 160/110 mm Hg.
Continue close maternal and fetal monitoring.

Anticonvulsant therapy[50]
If convulsion has occurred, use magnesium sulphate, intravenously or intramuscularly.
In cases of severe pre-eclampsia, consider magnesium sulphate treatment.

Fetal management
Prophylactic steroids if the duration of gestation is less than 34 weeks.
An initial ultrasonographic assessment of fetal weight on presentation.
Doppler ultrasonographic assessment of umbilical blood-flow velocity.
Regular cardiotocography (non-stress tests).
Ultrasonography at least twice a week for liquor volume.
Delivery on the best day in the best way.

Care after delivery
Continued close monitoring of the mother by experienced carers.
Careful fluid balance and early use of diuretics if fluid overload with pulmonary oedema is suspected.
Decrease dose of antihypertensive agents as indicated.
Stop anticonvulsant therapy after 48 h if stable.

Follow-up
Long-term follow-up to make sure that the blood pressure falls, and suitable referral if it does not.
Discussion about the illness and the significance for the future.
Referral for counselling to local experts and future planning.

leucoencephalopathy syndrome (PLES).[38] It is not a new diagnosis but a radiological description. The cerebral oedema may antedate eclampsia, because occipital-lobe blindness[39] can occur in the absence of eclampsia and is completely reversible.

Management

The management of pre-eclampsia is complicated by the presence of the fetus. Delivery is the ultimate cure, but management aimed at benefiting the mother may be detrimental to the fetus because premature birth is a significant cause of morbidity and mortality.[40] Therefore, the management of pre-eclampsia is based on a stepwise protocol: pregnant women are screened; those at risk are monitored; the maternal condition is stabilised; monitoring is continued; and the delivery is initiated at the best time for the mother and baby (panel 2).[41] In most instances, the rise in the blood pressure is the signpost to further management. However, care should be taken not to miss women presenting with other clinical features such as headache, abdominal pain, or general malaise. Any pregnant woman who feels unwell should be investigated for pre-eclampsia. There needs to be an easy quick system of referral from the community into the monitoring system.[5]

Assessment of the mother

If the blood pressure is slightly high but the results of other tests are normal, the woman does not have a significant risk at that time and can be referred back to the antenatal-care system. More than 60% of the women referred to an antenatal day unit met this description.[5] However, these women need continued follow-up because 15–25% will show progression to pre-eclampsia during the remainder of pregnancy.[42] The development of proteinuria, increasing oedema, signs of systemic involvement as assessed by a falling platelet count, a rise in uric acid concentration, abnormal liver function, or the addition of clinical symptoms such as headache, visual disturbance, or abdominal pain should prompt admission for further investigation and care.

Assessment of the fetus

The main disease process affecting the fetus is placental insufficiency leading to intrauterine growth restriction. It occurs in about 30% of pre-eclamptic pregnancies. Therefore, fetal investigations test growth and wellbeing.

Ultrasonographic assessment of fetal size at the time of the initial presentation with hypertension is a valuable one-off measurement to assess fetal growth. Growth restriction is not generally symmetrical, so assessment of the abominal circumference is the best method.[43] Low liquor volume is also associated with placental insufficiency and fetal growth restriction. Serial estimations of liquor volume can detect fetal compromise.[44] Umbilical-artery doppler assessment is also useful, and serial investigations can be used to follow pregnancies under treatment.

Cardiotocography (non-stress test) is the mainstay of fetal monitoring in most units. It can be repeated regularly and easily without the need for expensive equipment or highly skilled personnel. It gives information about fetal wellbeing at the time of assessment but has little predictive value.[44]

Antihypertensive agents

Hypertension is a primary risk factor for the mother. In the UK during the past 20 years, use of antihypertensive drugs has increased.[45] At the same time the frequency of cerebral lesions as a cause of maternal death has fallen, but the link may not be causal (table).[1]

If the blood pressure is above 160/100 mm Hg, maternal treatment aims to avert a severe hypertensive crisis, the need for further antihypertensive therapy, and admission to hospital.[11] Although many studies used groups of patients with various diagnoses, there is no evidence that these findings are any less relevant for pre-eclampsia than for chronic hypertension. Methyldopa and labetalol were the most commonly used drugs but all antihypertensive drugs seem to be effective. Some of the greatest benefits were seen with ketanserin, a selective serotonin-receptor blocker with α_1-blocker activity. Methyldopa was safe in long-term follow-up of the delivered babies.[46] However, atenolol is associated with an increase in fetal growth restriction,[47] and inhibitors of angiotensin-converting enzyme (ACE) are contraindicated because of unacceptable fetal side-effects; diuretics are contraindicated because they may cause growth restriction.[46] In later pregnancy, non-pharmacological approaches, such as rest in bed, physiological support, and biobehavioural training, have been used to manage mild to moderate hypertension. None have been proven beneficial.[11] By contrast, a meta-analysis of antihypertensive therapy has shown that early treatment decreases not only the frequency of hypertensive crisis but also the rate of neonatal complications such as respiratory distress syndrome.[48] There is, however, little evidence as to which antihypertensive drugs to use or the threshold of blood pressure that necessitates therapy.[11,46]

If the blood pressure is above 170/110 mm Hg, most obstetricians would use antihypertensive agents.[49] The most commonly used drugs are parenteral hydralazine, labetalol, and nifedipine, but trials persistently show that hydralazine is inferior to the other two drugs.[11] Once the blood pressure is controlled, expectant management is beneficial to the baby by reducing the risks of prematurity. The average extension of pregnancy is 14 days.[11] No single therapy can be successful in all patients, and increasing doses and combinations of drugs are generally required.[46]

In mild to moderate pre-eclampsia, the role of antihypertensive therapy is less clear. Various trials have shown overall benefit.[11,48] The starting blood pressures varied between 140/90 mm Hg and 150/105 mm Hg. A threshold for treatment of 150/100 mm Hg should give a reasonable balance between the number of women treated and the benefits achieved.[46] Of the drugs used, methyldopa, labetalol, and nifedipine are equally effective.

Anticonvulsant agents

If convulsions have occurred, magensium sulphate is the drug of choice.[50] However, no treatment will completely prevent seizures, which recur in between 5% and 20% of cases. Both intravenous and intramuscular regimens can be used; they are equally effective. The intramuscular route

Year	Cause				
	Cerebral	Pulmonary	Hepatic	Renal	Other
1970–72	25	8	5	3	6
1973–75	23	7	14	1	4
1976–78	21	4	5	0	3
1979–81	17	8	8	0	3
1982–84	21	3	0	0	1
1985–87	11	12	1	1	2
1988–90	14	10	1	0	2
1991–93	5	11	0	1	3
1994–96	7	9	3	0	1
Total	144	72	37	6	25

Causes of maternal death from pre-eclampsia and eclampsia in confidential enquiries over the past 26 years[1]

has the advantage of ease of use, although intravenous therapy may provide higher blood concentrations.[51] Both regimens use a slow bolus intravenous loading dose of 5 g over 20 min. If magnesium is given too quickly, cardiac arrhythmia or arrest can occur. With the dose regimens used by Duley and colleagues in the randomised trial,[50] an infusion of 1 g/h or 4 g intramuscularly every 4 h, there was no need for magnesium concentrations to be checked or for this facility to be available at all times.[50] However, in many parts of the world, infusions of 1–3 g/h are used.[51] Although checking of magnesium concentrations may be necessary when a higher infusion rate is used, toxic effects are unlikely when deep-tendon reflexes are still present. There has been concern about the concomitant use of magnesium sulphate and calcium-channel blockers.[11] This concern has been overstated, although there may be a synergistic effect and care should be taken. There is an increased risk of toxic effects of magnesium in renal impairment. Routine investigations of the mother include assessment of renal function, and it should be checked before or immediately after the start of magnesium therapy.

The role of prophylactic magnesium sulphate in pre-eclampsia is less clear. The risk of eclampsia in women with pre-eclampsia varies, and the relative risks and benefits of magnesium sulphate are unknown.[52] Magnesium sulphate can be associated with significant maternal morbidity and mortality. However, if a prophylctic anticonvulsant is to be used, magnesium sulphate is the drug of choice.[53]

Continuing management

In the absence of convulsions, continuation of the pregnancy should be considered in the interests of the baby, because the gestational age at birth influences the outcome for the baby more than any other variable.[40] If the duration of gestation is less than 34 weeks, prophylactic steroids should be given to induce fetal lung maturity.[54] However, there is uncertainty about whether betamethasone or dexamethasone should be used and the best dose and timing of dose.

If the pregnancy is to be continued, the situation should be constantly under review with close maternal and fetal monitoring, because lowering of the blood pressure will not attenuate the disease process. Underlying risks, such as abruption, remain.

Planning of delivery

Delivery is the ultimate cure for pre-eclampsia but most maternal deaths occur post partum.[1] The timing of delivery is critical. A rushed delivery in an unstable patient or a delay in delivery in a sick patient can add to the maternal risk rather than reducing it.

If delivery has been decided upon before 32 weeks of gestation, the practice in the UK is to deliver by elective caesarean section[41] although many centres throughout the world would attempt a vaginal delivery with varied results.[40] Labour can aggravate fluid overload and blood-pressure control, and vaginal delivery is successful in less than 50% of cases.[55] The choice of anaesthetic in caesarean section is important, because tracheal intubation can cause a rise in both systolic and diastolic blood pressure.[56] With an epidural or spinal block, care should be taken to keep the fluid load to a minimum. However, these methods can be safely used with appropriate supervision.[57]

After 34 weeks of gestation, a vaginal delivery is more likely. Antihypertensive therapy should be continued throughout labour. An epidural, by allowing adequate pain relief, can reduce the rise in blood pressure commonly associated with labour. It also allows a planned delivery and easy transition to caesarean section if necessary. After delivery, drugs containing ergometrine should not be used in the third stage of labour. Intravenous oxytocin is the preferred option.

Postpartum care

Continued close monitoring is required after delivery. An initial improvement with a relapse is commonly seen within 24 h of delivery. The woman should be cared for in a high-dependency area and should not be transferred to the postnatal ward until the test results begin to return to the normal range.

In the UK, the main cause of maternal mortality in pre-eclampsia is pulmonary oedema (table).[1] This complication occurs in about 6% of cases in severe disease.[58] It is aggravated by exogenous fluid given in the belief that plasma expansion is needed to improve cardiac output and lower the risk of renal failure. In fact, the average plasma volume deficit is only 600 mL, and the fluid replacement is commonly more than 6 L in 24 h, leading to fluid overload.[59] Also, renal failure is rare in pure pre-eclampsia and is generally associated with haemorrhage or sepsis.[58] It is becoming less common as a cause of maternal mortality (table)[1] and morbidity.[36]

Invasive monitoring is not generally necessary, and central venous pressure (CVP) lines can be misleading.[59,60] In pre-eclampsia, pulmonary oedema (as a result of increased interstitial fluid) can occur in the presence of a normal CVP. If a central line is used, the CVP should not be higher than 5 mm Hg or 7 cm water. If the CVP is higher, pulmonary oedema can occur. One of the complications of pulmonary oedema is poor oxygen saturation, so one of the best methods of monitoring fluid status is continuous measurement of oxygen saturation with a pulse oximeter.[41]

Most postnatal convulsions occur within the first 24 h after delivery, so anticonvulsant therapy is generally continued for 48 h after delivery. If the patient is well, especially if anticonvulsant treatment is being used prophylactically in the absence of any convulsions, this therapy can be stopped at 24 h. The dose of antihypertensive drugs should be lowered after delivery, depending on the blood pressure. Antihypertensive drugs may be necessary for some weeks after delivery. If blood pressure has not returned to normal by 6 weeks post partum, the patient should be referred for further investigation, because the cause may not be pre-eclampsia.

There should be a postnatal visit to assess the recovery of the woman and to discuss the significance of what happened and what might happen in the future. In many cases, the pregnancy has been traumatic for the woman and her partner, especially if the baby died. Time should be given to discuss the case fully with the woman and her partner and to go through the history of the case in the appropriate detail.

Women with severe pre-eclampsia have an increased risk of recurrence in their next pregnancy, but the disorder is generally less severe and manifests 2–3 weeks later than in the first pregnancy.

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