

THE MANAGEMENT OF SEVERE PRE-ECLAMPSIA AND ECLAMPSIA

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Severe pre-eclampsia and eclampsia are becoming rarer, so that individual experience in the management of these disorders is diminishing. The Cardiff Births Survey showed an incidence of moderate and severe pre-eclampsia and eclampsia of only 0.7% of deliveries during 1970-74 compared with 2.3% during 1965-69. In the decade 1965-74 there were nearly 60 000 singleton deliveries, of which only 40 were cases of eclampsia and 28 of these occurred in the first 5 years.

Nevertheless, in Great Britain, pre-eclampsia and eclampsia are the third commonest cause of maternal mortality after abortion and pulmonary embolism. In the Report on Confidential Enquiries into Maternal Deaths in 1970-72, 47 (13.2%) of the deaths were attributed to pre-eclampsia and eclampsia. In addition, in many cases where death was primarily caused by other disorders, such as pulmonary embolism, pre-eclampsia was a contributory factor.

Perinatal mortality may result from attempting to prolong a pre-term pregnancy in the presence of failing placental function or from prematurity if early delivery is undertaken. The relationship of perinatal mortality with birth weight is emphasized in the Cardiff data for 1970-74, when 58% of perinatal deaths in severe pre-eclampsia and eclampsia were in infants weighing less than 1500 g, but no deaths occurred in infants weighing more than 2500 g.

With good perinatal care not more than 2-3% of babies should be lost, but in association with eclampsia, which frequently results from defective antenatal care, perinatal mortality may be as high as 50%.

It is evident that there is scope for improving the management of severe forms of pre-eclampsia and eclampsia. In terms of experience an individual consultant obstetrician may only treat one patient with eclampsia every 1-2 years and individual members of the junior staff may not see more than half-a-dozen cases in their entire training period. Therefore, it is appropriate that the obstetrician should turn to his anaesthetic colleagues to establish a team to manage

such major and potentially lethal problems. It is also obvious that clear and co-ordinated plans of management should be established in advance, so that effective treatment can be instituted without delay in the acute emergency situation which so often arises.

AETIOLOGY

Pre-eclampsia/eclampsia is a condition peculiar to primates and to pregnancy and is rarely manifest before 24-28 weeks of gestation. The initiating factor is foetal or placental, or both, as shown by the limitation of the disease to pregnancy and the immediate post-partum period. The placenta, rather than the foetus, is likely to be responsible since the disease can occur in the absence of a foetus (as in hydatidiform mole), and can occur after foetal death *in utero* providing there is living placental tissue.

Since the condition may occur after delivery, it is more likely that the relevant factor is humoral rather than a reflex mechanism. Such a humoral substance might be endocrinological or immunological, but no specific factor has yet been identified.

The overall picture is one of failure of maternal adaptation to a changed physiological situation, the clinical manifestations being caused by disturbance of water and sodium balance, together with angiospasm associated with hypertension. It is difficult to determine the initiating or triggering factors in pre-eclampsia, but attention focuses on the renal glomerular changes, on fibrin deposition and on evidence of disseminated intravascular coagulation which probably occurs in varying degrees in all cases of pre-eclampsia. The features resemble the Schwartzman reaction and there is increasing, but largely unconfirmed, evidence that pre-eclampsia is explicable on a primary immunological basis with secondary ischaemia and disturbed homeostasis resulting in impaired placental and renal function.

CLINICAL FEATURES

Pre-eclampsia is characterized by lack of symptoms until an advanced stage, with the exception of oedema. With improving antenatal care, hypertension is often the first detected sign, and treatment may be

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initiated on this sign alone. Even by this stage many patients show excessive weight gain although clinical evidence of oedema is lacking. Proteinuria is a later feature and, being a manifestation of vascular and renal involvement, must be regarded as dangerous.

Other hypertensive and renal diseases not peculiar to pregnancy may pre-exist or, less commonly, develop during pregnancy and produce similar symptoms and signs. The more important of these are set out in table I. In addition, pre-eclampsia may be superimposed on pre-existing hypertensive disorders. From the point of view of practical management, all hypertensive disorders are dangerous and the hazards for the mother and foetus are similar. Also, the basic principles of treatment, with few exceptions, are similar.

The onset of symptoms, which include headache and photophobia, epigastric pain and vomiting, is ominous and, if neglected, eclampsia and coma may supervene.

Eclampsia is characterized by epileptiform convulsions. In the majority of cases there is evidence of pre-eclampsia, but sometimes the fits are unheralded, in which case other causes of convulsions require special consideration. The occurrence of eclampsia is not directly related to the severity of pre-eclampsia. In many patients an inherent cerebral dysrhythmia is present and there is a familial predisposition. Particular danger signs, in addition to the symptoms mentioned above, include a rapid increase in arterial pressure, decreased urine volume and local or generalized twitching with increased tendon reflexes.

TABLE I. *Classification of hypertension in pregnancy*

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- (1) *Hypertension peculiar to pregnancy*
(Onset after 24 weeks of gestation, excluding hydatidiform mole)
- (A) Pre-eclampsia
- (i) Mild BP > 140/90 mm Hg
or rise of 30 mm Hg systolic
or rise of 15 mm Hg diastolic
± oedema
- (ii) Severe Increased arterial pressure and proteinuria
± oedema
or diastolic pressure > 110 mm Hg
- (B) Eclampsia
Pre-eclampsia and convulsions
- (2) *Hypertension not peculiar to pregnancy*
- (A) Pre-existing (but not necessarily pre-diagnosed)
(Diastolic pressure > 90 mm Hg before 20 weeks of gestation and a subsequent increase not exceeding 10 mm Hg, without proteinuria)
- (i) Chronic ("essential") hypertension of unknown cause
- (ii) Secondary to chronic renal disorders:
e.g. Glomerulonephritis
Pyelonephritis
Hydronephrosis
Renal artery stenosis
- (iii) Secondary to cardiovascular disease:
e.g. Coarctation of the aorta
Polyarteritis nodosa
Disseminated lupus erythematosus
- (iv) Secondary to endocrine disorders or excessive dosage with corticosteroids:
e.g. Primary aldosteronism
Pheochromocytoma
Adrenocortical tumour
Diabetes mellitus
- (v) Secondary to other disorders:
e.g. Porphyria
- (B) Developing during pregnancy
e.g. Acute glomerulonephritis
- (3) *Pre-eclampsia superimposed on pre-existing hypertensive disorders*
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The fits are identical with grand mal epilepsy, with tonic and clonic phases. In the absence of effective treatment, fits occur with increasing frequency, and are succeeded by coma and respiratory and cardiac failure.

Fits occurring in late pregnancy and labour should be regarded as eclamptic until proved otherwise. The commonest source of confusion is epilepsy and it may be difficult to obtain a relevant past history if the patient is admitted in coma as an emergency. Transient localizing neurological signs may be present, but these suggest the possibility of other cerebrovascular pathology. Cerebrovascular accidents, with the exception of cerebral thrombosis, are not characterized by repeated convulsions.

Fits during labour may also result from over-breathing, especially in nervous patients or those poorly instructed in psychoprophylaxis. Excessive administration of fluids or syntocinon, or both, during labour in patients with severe pre-eclampsia or impaired renal function can result in water intoxication.

Eclampsia is unlikely to occur more than 24 hours post partum, unless there is retained placental tissue. Fits occurring more than 48 hours post partum are almost certainly not a result of eclampsia.

MANAGEMENT

The aims of management are to minimize the hazards to both the mother and the foetus until such time as the foetus stands a better chance of survival outside the uterus than inside, or until further prolongation of the pregnancy creates a threat to the mother's life. Generally, the foetal condition is a much more sensitive index of the disease process and evidence of failing placental function, as judged by failure of foetal growth, hormone assays and foetal cardiocography, is the principal factor indicating a need for termination of the pregnancy in the majority of cases. However, deterioration of the patient's condition in spite of appropriate therapy and the development of signs and symptoms mentioned previously, especially those associated with increased neuromuscular irritability, are portents of danger and the well-being of the mother becomes the dominant factor, irrespective of the condition of the foetus. Early effective treatment is imperative. The principal risks to the mother are:

- Cardiovascular complications, particularly cardiac failure.
- Cerebrovascular accidents.
- Disseminated intravascular coagulation.
- Renal failure.
- Eclampsia.

Should eclampsia occur or appear to be imminent, urgent treatment is required, since the prognosis for the mother is related to the number of fits. If the patient is not in hospital she should be attended by the obstetric flying squad.

General management

Intensive care facilities are required, either in a delivery unit or in a general intensive care unit. Trained medical and nursing staff must be in constant attendance, under the supervision of a consultant obstetrician and consultant anaesthetist.

Equipment must include a bed capable of head-down tilt, anaesthetic apparatus, including facilities for positive pressure ventilation, an electrocardiograph and, if possible, an automatic arterial pressure recorder.

Fits are precipitated by external stimuli, so that steps should be taken to reduce such stimuli by minimizing nursing and medical procedures. Whilst intense light should be avoided, the traditional procedure of nursing in a darkened room is dangerous as it hampers proper observation of the patient.

General care and monitoring are directed to the following:

Cardiovascular system. Arterial pressure recording at least quarter-hourly and preferably by an automatic recording apparatus, heart rate, electrocardiograph and central venous pressure. A careful watch must be kept for signs of cardiac failure.

Respiratory system. The airway must be kept clear using either an airway or, in cases of difficulty or deep coma, by endotracheal intubation. Frequent aspiration and changes of position are necessary. Antibiotic therapy may be indicated.

Renal function. The bladder is catheterized and the hourly output of urine is charted, together with the specific gravity or osmolarity. The degree of proteinuria and haematuria are noted.

Haematological investigations may include haemoglobin estimation, haematocrit, plasma osmolarity, electrolytes and urea, and a coagulation profile.

The foetal condition in severe cases is of secondary importance in the acute situation, but if the foetus is alive, continuous monitoring by cardiotocography is indicated and this may influence the timing and mode of delivery.

Drug therapy

Large series of patients with severe pre-eclampsia and eclampsia have been treated without maternal mortality by various therapeutic regimes which

included anti-convulsant therapy, hypotensive agents and pain relief or anaesthesia for delivery (Zuspan and Ward, 1965; Moir, Victor-Rodrigues and Willocks, 1972; Baskett and Bradford, 1973; Pritchard and Pritchard, 1975). Therefore the major residual problem is in selecting a technique which is most effective in minimizing perinatal mortality. To this end, particular attention should be given to avoiding excessive reduction of arterial pressure, which would result in impaired placental perfusion and, as far as possible, to avoid using drugs which may cross the placenta and have a significant effect on the foetus *in utero* or have a carry-over effect in the neonatal period, as is the case with diazepam used in large doses.

Generally, it is preferable to select drugs with which the staff are familiar, which have a wide margin of safety for both mother and foetus, and which are rapid and controllable in their action.

Primary therapy centres around sedation and anti-convulsants, reduction of arterial pressure and pain relief. Secondary therapy includes the use of diuretics, adjustment of electrolyte balance, treatment of coagulation disorders and, possibly, the administration of steroids.

Sedatives, hypnotics and anticonvulsants

There is now little place for the use of traditional sedatives such as bromethol, paraldehyde or barbiturates. The most widely used drugs at present are the benzodiazepines (diazepam, chlordiazepoxide), phenothiazines (promazine, chlorpromazine) and chlormethiazole. In some areas, particularly the U.S.A., magnesium sulphate is also used with satisfactory results.

Diazepam is a sedative and anticonvulsant with a wide safety margin. It is given by slow i.v. injection or in a dilute solution by i.v. infusion. Initially, diazepam is given into a large vein at a rate not exceeding 2.5 mg/min until the patient is drowsy, a state which is usually reached after a total dose of about 10 mg. This level of sedation is maintained by an i.v. infusion, usually in a dose range of 2–4 mg/h. Other drugs should not be given in the same infusion system. If the total dose exceeds 20–30 mg of diazepam, there is a risk of neonatal hypotonus and inadequate temperature regulation. As the neonate is unable to metabolize or excrete diazepam rapidly, the effects may be so prolonged that an exchange transfusion is necessary.

In an emergency, if the patient is having frequent convulsions, up to 10 mg of diazepam can be given initially over a period of 2 min. Alternatively, small

(25-mg) increments of thiopentone can be used. Muscle relaxants are not normally required, unless an endotracheal tube is necessary to safeguard the airway.

Phenothiazines depress the arousal mechanism, are used as adjuncts to other hypnotic agents and allow a reduction in dosage of these agents. In addition they have an anti-emetic effect. Their main use has been in the "lytic cocktail" (Menon, 1956). However, the original combination of drugs does not include a specific anticonvulsant, and therefore does not fulfil the essential criteria as effectively as more modern agents.

Chlormethiazole is a hypnotic and anticonvulsant of low toxicity. It is administered i.v. in a 0.8% solution, initially at the rate of 4 ml/min, until the patient is well sedated. The rate is then adjusted to maintain the desired level of sedation, usually at about 1 ml/min. Careful supervision and control of the dosage are essential, otherwise deep sedation and respiratory depression may occur. For this reason a drip control system or pump should always be used to deliver the solution. Unfortunately, chlormethiazole is relatively insoluble, and if therapy is required for a prolonged period an undesirable amount of fluid may be administered. Chlormethiazole and diazepam are commonly used together (but in separate infusion systems) to reduce the total dose of both drugs. No specific studies of effects on the foetus have been made, but Johnson (1976) reported neonatal apnoea and hypotonus when chlormethiazole was used with diazoxide.

Magnesium sulphate controls convulsions by blocking neuromuscular transmission. There is a decrease in acetylcholine at the neuromuscular junction and a reduction in sensitivity to acetylcholine at the end-plate. There is also reduced excitability of the muscle membrane (Del Castillo and Engbaek, 1954). Magnesium has a widespread action on the central nervous system from the cerebrum to the post-synaptic membranes. The extent of its action, which is related to its serum concentration, is therefore predictable. At serum magnesium concentrations of about 10 m-equiv/litre (5 mmol/litre), a muscle preparation fails to respond to single electrical shocks and at concentrations of 30 m-equiv/litre (15 mmol/litre), prolonged tetanic stimulation may only just elicit a response. Reflexes disappear at differing concentrations: tendon reflexes at 10 m-equiv/litre (5 mmol/litre), respiration at 15–20 m-equiv/litre (7.5–10 mmol/litre) and the corneal reflex at 30–35 m-equiv/litre (15–17.5 mmol/litre).

In clinical practice, the use of magnesium sulphate is aimed at achieving a blood concentration of 6–8 m-equiv/litre (3–4 mmol/litre). At this concentration the patellar reflexes are active (or the triceps reflexes, if the leg reflexes are blocked by extradural anaesthesia).

Most schemes of management are based upon that of Flowers (1965). An i.v. regime consists of 20% magnesium sulphate solution 4 g in 5 min, followed by 1 g/h. Alternatively, the i.v. priming dose may be followed by 4–10 g i.m., depending upon the body weight, every 4 h (Speroff, 1973).

Magnesium is distributed in the extracellular fluid and ultimately almost wholly excreted in the urine, although complete excretion may take some days. There is clearly a risk of overdose in patients with a low urinary excretion rate. It is important, therefore, to note the urinary output, and authors vary in their recommendations from maintaining a urinary excretion rate of 30 ml/h (Speroff, 1973) to 100 ml/h (Stone and Pritchard, 1970). It is advisable also to monitor serum magnesium concentrations. In the event of overdosage, a slow i.v. injection of calcium chloride 25% solution at a rate of 1–2 ml/min may be used. There is no doubt that the use of magnesium therapy can complicate the anaesthetists' management, since it increases the duration of action of muscle relaxants (Smith, Winkler and Hoff, 1942; Giesecke et al., 1968; Ghoneim and Long, 1970). It may also increase the hypotensive effects of regional anaesthesia (Hingson and Helman, 1956), although this is less certain.

Hypotensive agents

In acute fulminating pre-eclampsia and eclampsia it is necessary to select an agent which can be given i.v. and is rapid in its effect. *Hydrallazine* is the drug most commonly used, and exerts its effect through a general direct action on vascular smooth muscle (Goodman and Gilman, 1975). It increases renal blood flow, which may be advantageous, although there is no evidence of increased glomerular filtration. It also causes tachycardia and increases cardiac output. A rare toxic manifestation is a syndrome similar to systemic lupus erythematosus. *Hydrallazine*, 20 mg initially, followed by 5 mg at 20-min intervals can be given by intermittent i.v. injection, until the diastolic pressure is less than 110 mm Hg, followed by a continuous i.v. infusion by syringe pump, usually in a dose range of 2–20 mg/h, to control the arterial pressure. Thiazide diuretics potentiate the action of *hydrallazine*. Beta-blocking agents, such as *propranolol*

2–4 mg, enhance the anti-hypertensive effect and prevent the reflex tachycardia.

Undue hypotension is easily treated by elevation of the foot of the bed and by i.v. fluids. If control with *hydrallazine* is unsatisfactory, *pentolinium* 2–5 mg or a *trimetaphan* infusion (0.1%) will rapidly decrease the arterial pressure.

Diuretics

Diuretic therapy is indicated only if there is gross fluid retention, or if there is evidence of impending acute renal failure (urine urea less than 20 g/litre and specific gravity less than 1012), or, in the longer term, to potentiate the action of hypotensive drugs.

In acute situations a rapidly acting diuretic which can be given by i.v. injection, such as *frusemide*, may be indicated in an initial dose of 20–40 mg i.m. or i.v. and repeated doses can be given after intervals of 2–4 h, depending on the urinary output, osmolality and electrolyte status.

Osmotic diuretics act by decreasing tubular resorption of water and electrolytes, but are ineffective and contraindicated if there is gross renal impairment. They remove water and electrolytes from the tissues and contribute to reduction of intracranial pressure. *Mannitol* may be administered if a patient is oedematous and diuresis has already been established, for example with *frusemide*. If an oedematous patient has a low plasma osmolality and a reduced central venous pressure, an infusion of salt-free albumin or plasma protein fraction is helpful.

Dexamethasone may be of value in reducing cerebral oedema.

Beilin (1973) recommends a cautious approach to the use of diuretics because of the risks of producing excessive sodium depletion, pancreatitis and neonatal thrombocytopenia, and suggests that diuretics should probably only be used when control of arterial pressure is difficult or when there is cardiac failure.

Mode of delivery

The need for delivery is rarely so urgent that the patient cannot be sedated, assessed and properly prepared for operative delivery. Termination of pregnancy before 36 weeks is indicated if there is evidence of failing placental function, if eclampsia develops or if there is maternal deterioration in spite of treatment. After 36 weeks, persistent hypertension exceeding 150/100 mm Hg or persistent proteinuria generally indicate the need for termination.

When delivery is planned by the vaginal route, there is general agreement that extradural anaesthesia

provides the best method of pain relief (Craig, 1972; Moir, Victor-Rodrigues and Willocks, 1972; Speroff, 1973). Because of the possibility of coagulation failure, especially in eclampsia, it is essential to ensure that coagulation is unaffected before proceeding with an extradural block. Undue hypotension will lead to further impairment of placental perfusion. It is sufficient to decrease the diastolic pressure to less than 110 mm Hg and to prevent a further increase in pressure during labour, if necessary by a more extensive block. The autonomic blockade may be continued post partum.

In many obstetric hospitals, there may not be skilled anaesthetic or obstetric staff who can manage an extradural block. In that case, the commonly used methods of pain relief can be employed, that is, pethidine and inhalation analgesia, although it may be more difficult to control the arterial pressure. In severe pre-eclampsia it may be wise to avoid methoxyflurane because of its potential nephrotoxicity, although there is no evidence for this with the analgesic dose used.

SUMMARY

With improving standards of antenatal care, severe pre-eclampsia and eclampsia are becoming less common and experience in the management of these conditions is lessening. Co-ordinated plans for the care of patients should be established by obstetricians and anaesthetists working as a team. A suitable regime for drug therapy in severe pre-eclampsia or eclampsia is the following:

Initial management

Diazepam 10 mg slowly i.v.

Pethidine 100–150 mg i.m. or i.v. in incremental dosage, or extradural block, if analgesia is also required.

Hydrallazine 20 mg i.v. initially, followed by 5 mg at intervals of 20 min until the diastolic pressure is less than 110 mm Hg. Then, preferably by syringe pump in a concentration of 2 mg/ml, at a rate of 2–20 mg/h. If vomiting occurs this can be controlled by administration of atropine.

Subsequent management

Sedation and anticonvulsant therapy. Continue *diazepam*

Caesarean section should always be considered if the foetus is alive and of a maturity which suggests a reasonable chance of extrauterine survival, especially if comprehensive foetal monitoring is unavailable. If extradural analgesia has been instituted it can be continued, with the usual precautions for converting to a general anaesthetic if there is an inadequate block or unsatisfactory surgical conditions. However, general anaesthesia is used more commonly. If there is time, it is valuable to measure the central venous pressure, since pre-eclampsia and eclampsia are accompanied by hypovolaemia, and blood loss and replacement may provoke extreme changes.

Post partum

Anticonvulsant and hypotensive therapy should be continued, in decreasing doses for at least 48 hours post partum. If delivery was by Caesarean section and extradural analgesia was established, this should be continued as an effective method of pain relief after surgery.

and, in severe cases, institute *chlormethiazole* infusion.

Continue analgesia with *pethidine* or *extradural* block.

Control of hypertension by adjusting the dose of *hydralazine*. If tachycardia exceeds 120 beat/min give *propranolol* 2–4 mg i.v.

Plasma protein depletion with gross oedema is treated by administration of *salt-free albumin* or *plasma protein fraction*.

Diuretic therapy is indicated if there is gross oedema or signs suggestive of acute renal failure. Oliguria associated with increased blood urea may be a result of renal failure or dehydration. The latter should be evident from the patient's condition and central venous pressure, but i.v. fluids and *frusemide* 20–40 mg can be used as a therapeutic test. *Mannitol* reduces cerebral oedema and may be given if diuresis has been first produced with frusemide.

Potassium chloride is given if the plasma potassium decreases to less than 3 mmol/litre.

Heparin therapy is considered if there is clinical evidence of disseminated intravascular coagulation.

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