RES MEDICA
Journal of the Royal Medical Society

Pre-Eclampsia Toxaemia of Pregnancy

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Abstract
The toxaemias of pregnancy form a discrete clinical syndrome which has been recognised as a disease of pregnancy almost since the practice of medicine began. Their aetiology and pathogenesis are still unknown, and despite all the resources of modern medicine, there is no treatment more effective than termination of the pregnancy — a therapy which was discovered several centuries B .C. There is no question that the nature of the condition provides one of the most fascinating problems of contemporary medical research, but the urgency of gaining an understanding of the condition, and of evolving more effective therapy, is only seen by considering the damage actually done by the disease, and the toll it still takes of maternal and infant life.

Present day maternal mortality figures are approximately 0.4 deaths per 1000 births. Of these, 18% are due to pregnancy toxaemia, which is second only to abortion as the largest single cause of maternal loss of life. For the child, the risk of stillbirth or early neonatal death is more than doubled in toxaemia, compared with normal pregnancy. It is possible to calculate that the loss of infant life in United Kingdom which can be ascribed to toxaemia is about 3,000 deaths per annum. For comparison, the total number of deaths in road accidents is about 7,000 per annum. Thus pregnancy toxaemia can be taken to be responsible for nearly half as many deaths as our much publicised traffic problem.

ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Winter 1965-66, 5(1): 29-33
doi: 10.2218/resmedica.v5i1.449

PRE-ECLAMPSIA TOXAEMIA OF PREGNANCY

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Based on a dissertation read to the Royal Medical Society, on 5th November, 1965.

The toxaemias of pregnancy form a discrete clinical syndrome which has been recognised as a disease of pregnancy almost since the practice of medicine began. Their aetiology and pathogenesis are still unknown, and despite all the resources of modern medicine, there is no treatment more effective than termination of the pregnancy — a therapy which was discovered several centuries B.C. There is no question that the nature of the condition provides one of the most fascinating problems of contemporary medical research, but the urgency of gaining an understanding of the condition, and of evolving more effective therapy, is only seen by considering the damage actually done by the disease, and the toll it still takes of maternal and infant life.

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The actual incidence of the condition is difficult to assess, largely due to the problem of establishing a generally acceptable set of diagnostic criteria. Average figures seem to suggest an incidence of 10% in first pregnancies, and 5% in other pregnancies, but estimates as high as 25% of all pregnancies have been quoted.[1] Thus toxaemia of pregnancy is not simply a rare and interesting obstetric curiousity. It is a very real disease, responsible for considerable suffering, which deserves our close and critical appraisal.

Definition of Toxaemia

Toxaemia of pregnancy is strictly a syndrome, not a disease. It is characterised by three features — hypertension, oedema and albuminuria — and these three features define the condition. However, they do not all need to be present to justify the diagnosis, since in mild cases, albuminuria may be absent or minimal There are also three possible origins or foundations for the toxaemia, and these are pre-eclampsia, essential hypertension and chronic nephritis.

The classification becomes further complicated by the fact that quite apart from the toxaemia deriving from essential hypertension,

patients with essential hypertension suffer an increased risk of developing a superimposed pre-eclamptic toxaemia. It is possible for a patient to have essential hypertension throughout pregnancy without developing toxaemia, but the interesting question of whether the same may be said of pre-eclampsia cannot be answered.

The three conditions are commonly classed together since differentation between them, particularly in the late pregnancy, is often impossible, and since the treatment is largely identical, resolution is usually an academic point. There is, however, some basis for considering pre-eclampsia a discrete condition. In this type, the onset of toxaemia is often asymptomatic and usually occurs after the thirtieth week of pregnancy. It may advance slowly or rapidly, and all but the mildest form will produce histological changes in the liver, kidney and placenta. Severe pre-eclampsia will lead to eclampsia. This pattern is characteristic of the pre-eclamptic type of toxaemia, and forms the basis for the statement that pre-eclampsia can occur in the patient with essential hypertension. Subsequent discussion is confined to this type of toxaemia, since it seems possible that the basic pathology underlying it is also partly responsible for the production of the other toxaemias. However it should be emphasised that this is an assumption without solid foundation, and is not generally accepted.

Presentation of Pre-Eclampsia

Pre-eclampsia is a condition confined to pregnancy. The three primary features of toxaemia have been described, and in this form, the hypertension is usually the first to appear, followed by the fluid retention. Hypertension is commonly taken to be present when the blood pressure reaches 140/90, but since the B.P. during the second trimester may normally be as low as 110/70, a sudden rise from this to 130/85 could well represent the onset of toxaemia. It is therefore imperative that the blood pressure is recorded under identical conditions each time the patient attends for antenatal care.

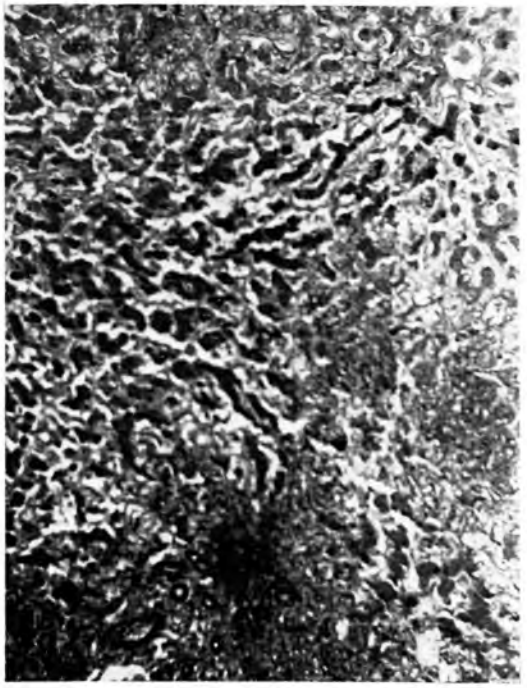
Fluid retention appears as a generalised oedema not to be confused with ankle-swelling, which is often present in apparently normal pregnancy. Tightness of the wedding-ring, or puffiness of the eyes is often the patients complaint, and although a worsening ankle oedema must be held to be suggestive of toxaemia, evidence of a non-dependent oedema is a much stronger clue. Albuminira is a late sign of pre-eclampsia and of little use diagnostically. Its degree does, however, carry considerable prognostic significance.

It is exceptional for a firm diagnosis of pre-eclampsia to be made on a single consultation. If the patient is attending regularly, a finding of a rise in blood pressure of 10 mm. diastolic, a complaint of oedema, or a weight gain of 3 lb. in two weeks requires that the patient be seen again within two or three days. If the findings are confirmed, the diagnosis of toxaemia should be made, and therapeutic measures instituted. This may sound easy, but one must remember that ankle oedema is common in pregnancy; urinary infection (producing a trace of albuminuria) is also common, and any anxiety will elevate the blood pressure. All three signs may thus co-exist without having any basis in toxaemia. Diagnosis is thus made from repeated routine checking of weight, blood pressure and the urine, and provided these tests are conscientiously carried out successful early detection can be achieved.

In the more severe case of pre-eclampsia other manifestations of the toxaemia are added — namely headache, visual disturbances, epigastric pain and vomiting, and the condition may proceed to frank eclampsia with episodes of convulsions, coma and then further convulsions. Even if left untreated, not every case of pre-eclampsia would proceed to eclampsia, but there is no way of predicting the course of the disease at the time of its onset and it is not possible to detect those destined for the severe type of toxaemia. Early diagnosis and careful observation is therefore necessary in all cases.

Pathology

The classical pathology of eclampsia is represented by changes in the liver and kidney which are quite characteristic. The liver is said to undergo a periportal necrosis in the first instance, but this of course may extend to a massive necrosis with liver failure. A midzonal necrosis is also seen in some cases. However it is the periportal lesion that is characteristic of eclampsia and it has been shown that it is caused by leakage of plasma into the space between the column of liver cells and its sheath of connective tissue, producing compression and necrosis of the cells.[2] The leakage is of blood rather than plasma in cases of haemorrhagic necrosis. Multiple small haemorrhages are also present beneath the capsule of the liver, and within the organ itself.



Liver In Eclampsia showing periportal necrosis (by courtesy of Mr. L. P. Mackenzie).

The kidney exhibits a characteristic glomerular change with endotheliosis, swelling of the endothelial cells and oedema of the interstitium. No abnormality of the basement membrane has been found. The placenta shows evidence of premature ageing with areas of infarction and fibrin nodes on the villi, but there are no changes characteristic of the disease. Elsewhere in the body, the lesions are those of capillary thrombosis and haemorrhage, and small haemorrhages are found generally.

Investigations into blood flow have shown that the kidney in pre-eclampsia has a low blood flow as a consequence of reduction in diameter of the afferent arteriole[3] and there is some evidence that the uterine and placental arterial supply is also diminished.[4] Blood flow to the liver, brain and limbs in pre-eclampsia has not been shown to differ from normal pregnancy, but in eclampsia, the cerebral blood flow is severely reduced[5]. Thus the pathology of the condition, together with the clinical manifestations appears to indicate that there is an arterial or arteriolar constriction in at least kidney and placenta which has given rise to an increase in peripheral resistance, and so to hypertension. The capillary haemorrhages and liver changes can be regarded as secondary to hypertension, and the eclamptic convulsions are almost certainly due to cerebral anoxia following arteriolar spasm.

The renal picture of a broadened pale renal cortex and congested medulla, with microscopy showing swollen glomeruli, immediately calls to mind the lesion of acute glomerulonephritis. The similarities, of course, go further—the presenting clinical signs in both conditions include hypertension, non-dependent oedema and albuminuria, and in severe glomerulonephritis, convulsions also occur. It is therefore necessary to bear in mind the possibility of pre-eclampsia having a related pathogenesis, and being essentially an immunological reaction to a sensitising agent derived from the foetus or placenta. However considerable difficulty arises when an attempt is made to explain the relationship of the odema to the hypertension, and in trying to correlate the degree of hypertension with the extent of renal damage. Nevertheless, some support is produced for immunological explanations of pre-eclampsia and although these do not hold widespread popularity, they should not be overlooked.[6,7]

Actiology

Before considering some of the other possible causes of pre-eclampsia, it is desirable to record some of the epidemiological findings that will have to be reconciled with any acceptable theory.

1. Pre-eclampsia appears more often in first pregnancies than in subsequent pregnancies.
2. Essential hypertension predisposes to it, and conversely, pre-eclampsia predisposes to the development of essential hypertension in later life.
3. Multiple pregnancies carry a higher risk of pre-eclampsia than normal pregnancies.
4. Hydatiform mole predisposes to pre-eclampsia.
5. Death of the foetus in utero is usually associated with improvement in the condition, but eclampsia can occur after delivery of the foetus and expulsion of the placenta.

There is no justification for assuming automatically that since pre-eclampsia is a disease of pregnancy alone, its origins will be found in

the products of conception. Gross changes occur in many organs during pregnancy, and these must be regarded with every bit as much suspicion as the uterine contents. Nevertheless, with some grounds, many workers believe in the production of a pressor substance by the placenta, and the liberation of this material into the maternal circulation, causing the hypertension. By analogy with the kidney, the concept of the "Goldblatt placenta" has arisen, but positive evidence of a humoral vasopressor material liberated as a result of uterine or placental ischaemia is sadly lacking. It is known that the plasma renin level is elevated during pregnancy, but there is no evidence that the uterus or placenta is responsible for this, nor that the elevation is greater in toxaemic patients than in normal pregnancy.[8] Investigation of the steroid hormones in toxaemia has given conflicting results, but the general feeling seems to support an elevation of the 17 - hydroxysteroid output, with a reduction in the adrenocortical response to A.C.T.H. even lower than in normal pregnancy.[9,10] It has been suggested that the ratio of mineralocorticoid/glucocorticoid hormones is elevated in toxaemia[11] but current work all seems to refute the proposal that aldosterone production in toxaemia is higher than in normal pregnancy[12,13] An elevation of aldosterone output would, of course, be an excellent preliminary to rationalising the salt and water retention.

There are also published works on the presence of an anti-diuretic material found in pre-eclamptic patients sera, suggesting a posterior pituitary-like hormone as the causative agent, but in spite of the natural tendency to think of the posterior pituitary when concerned with a problem of vasoconstriction and water retention, this too has led nowhere.[14,15]

Recently, great interest has centred on the monoamines, and in particular 5 - hydroxytryptamine. The discovery of reduced monoamine oxidase activity in the placentae of pre-eclamptic patients led to the theory that 5 - hydroxytryptamine accumulated in these patients, producing vasoconstriction.[16] Since monoamine oxidase activity is known to be related to oxygen tension[17] this vasoconstriction, by lowering placental oxygen tension, would reduce monoamine oxidase activity still further and so a vicious circle would be set up. However the monoamine oxidase inhibitor drugs do not appear to precipitate pre-eclampsia, as they might be expected to do if this theory were valid, and there is no positive evidence to support the contention that these drugs are unable to cross the "placental barrier". In any case, a paper published recently failed to confirm the basic finding of reduced monoamine oxidase levels.[18]

Although pre-eclampsia amply justifies its title of "the disease of theories" there is no question that current thought is focused on a humoral origin of the hypertension, related to ischaemia of the uterus or its contents. However, although the idea is not new[19,20] the importance of variation in sensitivity of the blood vessels to the known pressor agents does not seem to have received the intense experimental investigation that it warrants. There are two possibilities.

1. That the blood vessels in the pre-eclamptic patient are inherently more sensitive to a pressor material produced by the uterus or its contents in all pregnancies.
2. That the uterus in pre-eclampsia is liberating into the maternal circulation a material which is not in itself a pressor substance, but increases the sensitivity of the blood vessels to the known pressor materials. The possible implication of monoamine oxidase in the actiology of pre-eclampsia renders one very conscious of the precedent provided by the action of the anti cholinesterase drugs at the neuromuscular junction.

There is no question that the influences — notably endocrine influences — on the sensitivity of blood vessels to substances such as the catechol amines, serotonin, angiatensin and the posterior pituitary hormones are worthy of intense investigation. Progress in research into essential hypertension must be closely followed by those interested in pre-eclampsia, and it could be that the two conditions have much in common.

Management of Pre-Eclampsia

A woman admitted to hospital with mild or moderate pre-eclampsia is usually confined to bed, given a sedative such as phenobarbitone or amytal, and nothing more. Some obstetricians also restrict the patient's salt intake. Complete bed rest and sedation are designed to provide the best environment for peace of mind and a general absence of the emotional strains of daily life, but of course, steps must also be taken to isolate the patient from any sources of personal worry if these exist. In severe cases a check on urinary output is necessary, but in the majority observation of blood pressure and weight will show the success of these measures. Bed rest

alone, by virtue of being a horizontal position, will reduce ankle oedema, so this must not be regarded as an index of the response to treatment.

For the minority of patients in whom this regime is unsatisfactory, the use of hypotensive drugs may be necessary. The rauwolfia and veratrum alkaloids have been used — reserpine in particular is a good drug for the milder degrees of hypertension. Severe cases will require the use of guanethidine in conjunction with a thiazide diuretic, since it is imperative to bring the blood pressure down to less dangerous levels. One hopes that the risk of eclampsia is correspondingly diminished. However the effect of the more potent anti-hypertensive and diuretic drugs on the prognosis for the child has been disappointing, and it appears that this is largely due to their small effect on uterine blood flow and therefore on placental supply.

The obstetric management of pre-eclampsia can demand agonising decisions. It may be said that as pregnancy advances to term, pre-eclampsia will tend to become more severe, and the ageing placenta will fail to meet the requirements of the foetus. On the other hand, the foetus in pre-eclampsia is commonly smaller than average, and early induction of labour is liable to produce a very small baby, exposed to all the risks of prematurity. The problem is therefore one of when to induce, and no hard and fast rules are available. Assessment of the baby's size is usually carried out clinically and some idea of placental function may be gained from the urinary pregnanediol output, but experience remains the best foundation for making the decision. Induction before 36 weeks will be necessary in patients with severe hypertension and albuminuria, since here the prognosis for the infant is better than that for the foetus in utero. The correlation between albuminuria and prognosis has been mentioned earlier. Nevertheless, the great majority of cases can be left to 38 or 39 weeks, when induction should usually be carried out. The conventional methods of induction are used, and this is not the place to discuss the relative merits of these. But it is not out of place to add that the general rule of failed oxytocin induction being an indication for Caesarian section is in no way invalidated by toxaemia.

The management of imminent or frank eclampsia is a standard procedure and there is little to be gained from reiterating it here. It is obvious that pre-eclampsia is a condition where it is vital under present circumstances to concentrate on early diagnosis and the prevention of eclampsia, rather than the treatment of eclampsia itself. Surveys of maternal mortality in toxaemia indicate that nearly 50% of the deaths could have been avoided with early diagnosis and treatment. The size of this avoidable mortality is in part due to patients who, for one reason or another, have failed to seek medical attention, but it still represents an unnecessary loss of life, and the importance of every pregnant woman receiving anti-natal care must be firmly impressed on the general population. Nevertheless, even with the best care available, the treatment of toxaemia seems inadequate for the mid-twentieth century, and it looks as if permutations and modifications of present methods will provide nothing but trivial improvement. It is likely that the solution will eventually come from the endocrinologist who is investigating the problem at the fundamental level, and one would hope that from this, an efficient therapy will be developed to banish this disease of theories from our maternity hospitals.

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