PRE-ECLAMPTIC TOXAEMIA*

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During the course of this century maternal mortality has fallen from a peak of 7.6 in 1918 to well below 1 per 1,000 births to-day, but nevertheless a study of the Registrar-General's Review (1956-7) reveals that a third of these deaths are still due to toxæmia of pregnancy.

Whilst information of the maternal cause of stillbirths and neonatal deaths is scanty, Baird, Walker, and Thomson (1954), in analysing 1,008 foetal deaths, found that 20% were due to toxæmia and accidental haemorrhage. A total loss of child life in Great Britain, as shown in a report of the Ministry of Health (1949) for all toxæmias, varies between 25 and 40%, while 15 to 20% of all infant losses are associated with toxæmia.

In this paper the theories regarding the aetiology of toxæmia of pregnancy are omitted, as a general treatment of the subject, with particular reference to known clinical facts, is of greater import.

Gemmell, Logan, and Benjamin (1954), in analysing a large series of pregnancies, found that 8.5% of primigravidae and 4.2% of multigravidae developed toxæmia; this is close to the commonly accepted 10% for all pregnancies. The incidence increases in primigravidae over the age of 30 and in multigravidae over 40, whilst it recurs in subsequent pregnancies in 30 to 40% of patients.

Few to-day consider that chronic renal damage is a sequela of toxæmia, and most workers, including Theobald (1933, 1955), Isenhour *et al.* (1942), Barnes and Browne (1945), and Kellar (1950), are agreed that toxæmia does not predispose a patient to chronic hypertension. Light (1948), Gibson (1956), and others believe that the degree of severity and duration of toxæmia do not appear to influence the production of residual hypertension. Browne and Sheumack (1956) conclude that if a patient does not belong to a hypertensive family she will not develop residual hypertension. They also consider that it is probable that in patients who develop hypertension the toxæmia does not cause the hypertension, but simply unmasks the tendency. Primary hypertension therefore appears to predispose a patient to pre-eclamptic toxæmia.

While we may not be able in the course of a pregnancy to cure toxæmia, much can be done to alleviate it. The aetiology is obscure; the treatment must therefore be empirical, and the management of a case should be dependent upon the consideration of the immediate maternal and foetal prognosis, the later prognosis being ignored. This fact should be the basis of our course of action in all phases of this disease. We know that if the pre-eclamptic state increases in intensity there follows a risk of the two major catastrophes of the disease—eclampsia and accidental haemorrhage.

Eclampsia

Eclampsia rarely occurs as a fulminating condition, but almost always follows upon a pre-eclamptic state of varying duration. In our series of 110 cases 90% were of this

type, only 10% being of the acute type, presenting no obvious history of previous toxæmia.

The aim of treatment in eclampsia is to stop the convulsions, as the immediate prognosis for both mother and child depends on this. Sedation and hypotensive drugs are used with this end in view. When the condition is under control the pregnancy should be terminated as soon as practicable, preferably by the natural route.

All cases of eclampsia should be removed at once to hospital in view of the special nursing and constant medical supervision that are needed. Even in a rural area such as ours (Caernarvonshire, Anglesey, and Merioneth), entailing a journey of 50 to 60 miles (80 to 96 km.), I believe this is the best policy. We find that valuable time is lost by the use of the "flying squad," and therefore advocate transfer to hospital, following the administration of morphine, $\frac{1}{2}$ gr. (32 mg.), and atropine sulphate, 1/60 gr. (1 mg.). In hospital the obstetric team can follow a standardized routine of treatment, and by always using the same course of action assessment becomes easier.

As implied, our method of treatment is that of a modified Stroganoff regime—morphine, chloral, and bromide, supplemented by intravenous magnesium sulphate and calcium gluconate. In cases with marked oliguria 50-100 ml. of 50% dextrose is infused intravenously. A strict time-table is adhered to and sedation closely controlled. Labour is induced as early as possible: in our series of 110 cases only one was subjected to caesarean section because of maternal distress due to eclampsia.

Other effective methods of sedation are the bromethol ("avertin") technique advocated by Dewar and Morris (1947) and that of sodium thiopentone described by O'Donel Browne (1950). Both methods have produced effective lowering of maternal loss, and this is now rivalled by the use of hypotensive treatment ("veratrine") as advocated by Stern and Burnett (1954). Comparison of the statistics relating to the various forms of treatment would be helpful.

From Table I it appears that the outcome of our treatment compares reasonably well with other methods, especially as of the five maternal deaths in our series three occurred in the very early days of the obstetric service in patients who were moribund on admission, and one of whom proved to have bilateral congenital cystic disease of the kidneys. Only two deaths have occurred during the last 15 years. Our method of treatment therefore appears to be suitable for application in our area.

TABLE I.—(Stern and Burnett, 1954)

All Authorities	Total Cases	Maternal Mortality	Recorded No. of Infants	Foetal Loss
Sedation	1,071	7.56%	840	29.17%
Bromethol	149	4.03%	89	32.58%
Veratrine	498	1.81%	123	28.46%
Sedation: St. David's Hospital, 1938-56	110	4.5%	102	28.4%

TABLE II

Method of Treatment	Total Cases	Maternal Mortality	Foetal Loss	Recurrence of Fits after Commencing Treatment
Bromethol:				
Dewar and Morris (1947)	44	4.5%	30.6%	6.8%
Dewar (1947-53) ..	39	2.5%	15.7%	7.7%
Sodium thiopentone:				
O'Donel Browne (1950) ..	18	5.5%	27.2%	22.2%
Rotunda (1950-1) ..	26	7.6%	33.0%	13.5%
Krishna Menon (1953) ..	75	16.0%	40.0%	9.5%
Sedation:				
St. David's Hospital Dewar and Morris (1939-43) ..	110	4.5%	28.4%	34.0%
	88	20.5%	41.5%	59.3%

*Read at a combined meeting of the Sections of Obstetrics and Gynaecology and of General Practice at the Annual Meeting of the British Medical Association, Newcastle upon Tyne, 1957.

A significant feature is demonstrated in Table II in the low incidence of the recurrence of fits after the beginning of treatment with bromethol as compared with the other series. This reduction in the recurrence of fits should therefore be considered when instituting treatment of the eclamptic patient, as such recurrence increases the danger to mother and child.

The most effective method, however, of reducing fatalities from eclampsia must surely be to reduce the incidence of the disease. In our country area during the last five years (1952-6) 20 cases have been seen as compared with 42 during the five-year period 1942-6.

Accidental Haemorrhage

Accidental haemorrhage is the other acute condition associated with severe toxæmia, and in our experience the concealed accidental haemorrhage which is severe, creating an immediate state of emergency, is a sequela to a fulminating type of toxæmia. The sudden elevation of the blood pressure results in a spasm of the spiral arterioles in the decidua, leading to disruption of the placenta and haemorrhage.

Immediate and full treatment of such cases is essential to relieve shock and to assess the fibrinogen level. Our aim is to deliver the child within six hours of the onset of the disease and if necessary by caesarean section. The intensely toxic state causing the placental disruption and shock causes also a gross renal injury or "renal concussion" that may lead to intractable conditions such as renal cortical necrosis. The work of Sheehan (1955) on this subject is well known, and his more recent suggestions of the use of cortisone in the treatment of renal cortical necrosis may give us a gleam of hope.

Unfortunately, the fulminating toxæmia appears suddenly and unexpectedly, often resulting in this intense emergency and occasionally eclampsia; thus antenatal care fails to give warning and so prophylaxis is uncertain.

More common, however, are the small symptomless haemorrhages and infarcts that occur in established toxæmia, leading by repeated episodes to an accumulative destruction of placental tissue, resulting in placental insufficiency of varying degrees. This latter is likely to happen when the blood pressure rises to 160/100 or more, and is a truly dangerous phase for the infant, leading to intra-uterine anoxia and causing under-development or even death of the foetus *in utero* or during labour, occurrences which, I believe, are avoidable with adequate antenatal care and supervision.

It is a common practice among practitioners to ignore a high first reading of blood pressure, and to take the blood pressure again after a period of rest, and if this is lower to record it as the true level. In our experience this is wrong, for if the blood pressure rises significantly with little excitement it is evidence of an instability that is characteristic of the patient who is either hypertensive or potentially so. We find that such cases, even when at rest in hospital, show distinct variations in the blood-pressure level when this is recorded at intervals each day. These are the patients that need careful watching, for if the blood pressure rises to 160/100, and if the rise is sudden, there is a risk of arteriolar spasm in the renal glomeruli and in the decidua, leading respectively to albuminuria and placental damage. The appearance of albumin in the urine in such cases is therefore a grave warning that the life of the foetus is in danger.

Undoubtedly a high percentage of foetal loss results from this syndrome—a labile hypertension in pregnancy with superimposed toxæmia. It is essential that this condition be recognized early and carefully observed for prolonged periods in hospital. All patients with a blood pressure of 140/90 at the first visit, or who show later in pregnancy a rise above their normal, should be booked for hospital confinement and have the variations in their blood pressure checked as in-patients.

Imminent Eclampsia

Toxæmia may remain static or may gradually deteriorate, leading to a condition bordering on eclampsia—imminent eclampsia. This is characterized by a blood pressure of 160/110, oedema, albumin, oliguria, and symptoms such as headaches, visual changes, and epigastric pain. In such cases our action must be to prevent convulsions developing and to relieve the toxæmic state. Isolation with deep sedation is urgently needed, and if there is no improvement within 48 hours more active measures become necessary. Late in pregnancy this means the surgical induction of labour.

A dilemma arises, however, when this severe toxæmic state occurs before the 36th week of pregnancy. In such cases the foetus may die *in utero* if left too long, and if labour is induced the child will be small and will have to face the hazards of birth. With this degree of toxæmia we have the worst possible material—intense disease and a small immature infant. Even when pregnancy is terminated by caesarean section, various authors have noted a foetal loss of from 20 to 50%. In our experience, when the caesarean section is carried out under local analgesia and thiopentone is administered at the stage of opening the lower segment.

TABLE III

Weight	No. of Infants	Died
3 lb.-4 lb. 6 oz. (1.36-1.98 kg.)	15	2
4 lb. 7 oz.-5 lb. 8 oz. (2.01-2.5 kg.)	13	1
5 lb. 9 oz.-6 lb. (2.52-2.72 kg.)	7	
Total	35	3

the infant's chances of survival are much improved. In our series, extending over the last eight years, 35 patients were delivered in this way by caesarean section because of the severity of the toxæmia. Only three infants (8.5%) succumbed (Table III). In 20 comparable caesarean sections conducted under general anaesthesia the infant loss was 30%.

Discussion

How can we avoid eclampsia, accidental haemorrhage, and imminent eclampsia—those conditions that are responsible for a third of all maternal deaths and a quarter of all foetal wastage?

Workers such as Hamlin (1952), in Australia, and Dawson (1953), in New Zealand, have shown that strict attention to antenatal care leads to a significant lowering of the incidence of eclampsia and to a 50% reduction in foetal loss. To attain this, early detection of toxæmia is essential, together with early admission to hospital for complete and prolonged observation and treatment.

The early recognition of toxæmia is of paramount importance. A patient's usual blood pressure having been ascertained—and before the fifth month it should be below 140/90—any subsequent deviation above this level, however small, must be regarded with the greatest concern. This, with even slight pretibial pitting, warrants strict supervision in hospital. In our scattered antenatal clinics we have not been able to rely on the patient's weight as a guide, but the tightness of the wedding-ring and of the pretibial tissue is a reliable and early sign of fluid retention. Symptoms of headaches and visual disturbances are later indications of toxæmia, whilst albumin in the urine is a real danger signal.

Experience teaches us that under careful hospital supervision toxæmia can be controlled, be it primary or superimposed on hypertension. Our aim in all cases must be to keep the blood pressure below the danger level of 160/100: above that level the risk to both mother and child becomes really serious.

If the incidence of eclampsia is to be lowered and the foetal and maternal deaths from toxæmic causes are to be avoided, it is necessary to maintain a constant watch—with frequent blood-pressure and foetal heart recordings—on all

suspicious cases. This ideal can be attained only by the admission of all such cases to hospital.

The early recognition of toxæmia depends upon a routine antenatal service designed to be comprehensive. In this respect we believe that in our rural area, covering the two counties of Caernarvon and Anglesey, and since 1949 most of Merioneth, such a service has been organized. It is unique, in so far that since the inception of the service in 1938 the obstetric unit, based at St. David's Hospital, Bangor, has been responsible for all the local authority antenatal clinics.

Ten local authority clinic centres, at distances varying from 20 to 50 miles (32 to 80 km.) from the hospital, are administered by the county health departments, through the health visitors and district midwives, but all are conducted by the obstetric unit medical staff. In this way I believe we have achieved not only a continuity of treatment but also, what is equally important, uniformity of assessment of patients throughout a scattered rural area with a population of over 200,000.

In Tables IV and V, Merioneth has been excluded, as Anglesey and Caernarvonshire are true catchment areas and have co-operated fully since 1938.

The development of the obstetric service in the area may be seen from Table IV. An increasing proportion of mothers have been supervised in the antenatal clinics, and

TABLE IV.—*Anglesey and Caernarvonshire*

Period	Total Registered Births	First Clinic Attendances as Percentage of Total Births	Hospital Admissions per 100 Total Births		Maternal Deaths from Toxaemia per 1,000 Total Births
			For Toxaemia	For Eclampsia	
1938-41	9,811	20.9	1.8	0.12	2.44
1942-6	14,101	50.6	3.3	0.30	0.64
1947-51	14,248	62.1	4.3	0.25	0.56
1952-6	12,435	68.1	6.3	0.16	0.32

concurrently there has been an increasing resort to hospital admission for cases of toxæmia. This in turn is reflected in a marked lowering in the incidence of eclampsia. (From the early 1940's onwards it is safe to say that very few cases of eclampsia in the area are not admitted to hospital, so that the incidence can with confidence be assessed from the admission rate.)

From Table IV we can see, too, how increasing admission to hospital for toxæmia has resulted not only in fewer cases of eclampsia but also in a marked fall in the maternal mortality of the area from toxæmia and its associated conditions.

TABLE V.—*St. David's Hospital*

Period	Admissions for Toxaemia	Stillbirths in Hospital to Toxaemic Mothers	Percentage of Toxaemic Admissions Relating to Stillbirths
1938-41	180	43	23.9
1942-6	469	72	15.3
1947-51	610	57	9.3
1952-6	785	56	7.1

Table V gives some indication of the outcome as it affects the infant. The total number of stillbirths of toxæmic origin in the hospital unit has remained static, though in relation to the number of cases of toxæmia admitted there is a gradual fall. In a large proportion of these stillbirths recorded as due to toxæmia the foetus was dead *in utero* on admission, and those cases in which the blood pressure was raised were classified as of toxæmic origin.

However, of the 1,293 toxæmic mothers admitted into hospital during the antenatal period in the nine years 1948-56, a total of 1,491 infants were delivered. Of these, 94 were stillborn and 52 died within the first month—a total of 146 infants lost, a gross percentage of 9.8. This included 15 macerated and 15 abnormal infants. Dawson (1953), in his New Zealand series with 579 infants born of toxæmic mothers, showed an infant wastage of 8.8%. In his most

recent series of 170 infants wastage was 4.1%. Gibson (1954), in a total of 1,516 births, found a gross wastage of 15.9%, and Theobald (1955), in his series, 16.6%.

The average duration of the pregnancies of the 146 infants lost in our series was 35 weeks, which is similar to Dawson's findings.

To some extent the improved outlook for the baby may be due to the fact that an increasing proportion of the toxæmic cases admitted were of the less severe degree. The foetal wastage that is still occurring, including many already dead *in utero* on admission, indicates that in some cases either the patient does not avail herself of the antenatal service or conservative treatment at home is being prolonged beyond the danger point. In the light of our experience we feel that earlier termination of pregnancy would be the means of further reducing the wastage from stillbirths. This appears to be the obvious way to forestall such accidents as intra-uterine death of the foetus: the 35th week of pregnancy appears to be critical for the child in toxæmia.

Conclusions

A comprehensive antenatal service under the supervision of the obstetric unit of an area is advocated as a means of preventing the development of the severe degrees of toxæmia and reducing maternal and foetal mortality.

Booking for hospital confinement is recommended for all patients with an initial blood pressure of 140/90 or over, and admission to hospital for observation at the first sign of a deviation from their normal.

The importance of a regular routine for the treatment of eclampsia is stressed, and it is advocated that those methods giving the greatest reduction of incidence of fits be used.

Caesarean section under local analgesia and thiopentone gives the best prognosis for the immature infants in severe toxæmia.

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"Humane Technique in the Laboratory" is the title of volume 6 in the Laboratory Animals Bureau's series of *Collected Papers*. The volume contains papers and abstracts from a symposium held at Birkbeck College last May by the Universities Federation for Animal Welfare. Professor P. B. MEDAWAR, F.R.S., in a foreword, writes: "What is at once clear from this symposium is that improvements in the care of animals are not now likely to come of their own accord, merely by wishing for them; there must be research on methods of research." This volume is obtainable from the Bureau, M.R.C. Laboratories, Holly Hill, Hampstead, London, N.W.3, price 10s.