Middle Articles

FOR DEBATE . . .

Fibrinolysis in Pre-eclamptic Toxaemia of Pregnancy

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Summary: Plasma fibrinolysis is much reduced in normal pregnancy but is the same in women with toxaemia or hypertension, though urinary fibrinolysis is lower in them. The evidence suggests that in toxaemia there must be in addition a slow state of intravascular coagulation. Fibrinolytic inhibitors were found to be normal in this series, though in pregnancy there are raised levels of antitrypsin, α_2-macroglobulin, and β-lipoprotein. β-Lipoprotein levels in non-pregnant patients show a correlation with euglobulin lysis times and with inhibitor units.

Introduction

Immunofluorescent studies of renal biopsies taken from patients with toxaemia of pregnancy show that the swollen endothelial cells within the bloodless glomeruli contain fibrinogen or fibrin (Morris *et al.*, 1964). Gammaglobulin and complement cannot be shown, so that an immunological reaction as the cause of the fibrin deposition seems unlikely. Fibrin is probably deposited in the glomeruli as a result of a slow process of intravascular coagulation (McKay, 1964), which coincides with the considerable reduction of fibrinolytic activity in the renal endothelial cells that is found in pregnancy. The placenta and decidua contain more thromboplastic activity than any other organ. Thromboplastin may enter the circulation either from placental infarcts, which appear to be more common in toxaemia (Maqueo *et al.*, 1964; Wentworth, 1967), or by release from trophoblastic cells, which have been found in the circulation as early as the eighteenth week of gestation (Douglas *et al.*, 1959).

It has been suggested that placental insufficiency may lead to a state of chronic intravascular coagulation and that filtered fibrin leads to the changes in the renal glomeruli (Vassalli and McCluskey, 1965). Laboratory studies of coagulation are not sensitive enough for detection of an insidious process of intravascular coagulation, though reduced platelet counts (Morris *et al.*, 1964) and raised levels of cryofibrinogen have been reported (Shainoff and Page, 1962 ; McKay and Corey, 1964). Populations with a high prevalence of hypertension (Hatten, *et al.*, 1964) are known to have an increased incidence of toxaemia. One possible explanation of this might be that the hypertension leads to placental separation and other forms of placental degeneration and that this might lead to chronic intravascular coagulation and toxaemia. To investigate this hypothesis we have compared the fibrinolytic system in patients with normal pregnancies at term with those with hypertension appearing late in gestation or with more definite toxaemia.

Methods

Blood specimens were obtained from non-pregnant control subjects, from 23 patients during normal pregnancy at 36 weeks at least, from 20 patients admitted to hospital for hypertension appearing towards term, and from 23 patients with pre-eclamptic toxaemia, defined as proteinuria together with oedema or hypertension or both. The following estimations were made: platelet counts, recalcified plasma clotting times, plasma fibrinogen and cryofibrinogen (citrate) levels, together with assay of euglobulin lysis times and of fibrinolytic activity, and serum for radial immunodiffusion assay of β-lipoprotein and α_2-macroglobulin.

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Techniques

Plasma fibrinogen was assayed by the method of Quick (1951), the clot being dissolved in sodium hydroxide and assayed with Folin–Ciocalteau reagent against a tyrosine standard. Normal (non-pregnant) levels are 100–400 mg./100 ml.

Cryofibrinogen (citrate).—The precipitate obtained from 2 ml. of citrated plasma at 4° C. for 48 hours was washed in cold saline and then assayed as for fibrinogen and expressed as mg./100 ml.

Euglobulin lysis time was estimated by Von Kaulla's (1963) method, slightly modified by one of us (I. S. M.). The euglobulin lysis time can be expressed in units by multiplying the reciprocal of the lysis time in minutes by 10,000. A logarithmic plot of lysis time against units of activity shows a linear relationship.

Fibrinolytic inhibitors were estimated according to the method of McNichol *et al.* (1963) and are expressed as units. Normal (non-pregnant) patients have levels of 40–120 inhibitor units.

Urine fibrinolytic activity was assayed on fibrin plates by comparison of serial dilutions of urine against a urokinase standard. The activity is expressed as Plough units per 100 mg. of creatinine, normal non-pregnant levels being over 200 units.

Serum levels of α_2-macroglobulin and β-lipoprotein were estimated by radial diffusion (Mancini *et al.*, 1964) in agar plates containing Baxter specific antisera. Normal levels of β-lipoprotein for control normal sera were taken as 300 mg./100 ml. (checked by a chemical technique) and for α_2-macroglobulin as 200 mg./100 ml.

Results

No differences in platelet counts or in the mean or range of plasma fibrinogen levels were found among the three groups (Table I). On the other hand, significantly higher levels of cryofibrinogen (the early breakdown product of fibrinogen) were present in the patients with hypertension and toxaemia.

There was no difference among the groups as regards fibrinolytic activator activity or fibrinolytic inhibitors (Table II), but urinary fibrinolysis was particularly diminished in the patients with hypertension or toxaemia (Table I). A few patients had

TABLE I

	Normal Pregnancy	Hypertension	Toxaemia
No. of cases	23	20	23
Platelets (10^3/cu.mm.)	140–420	170–480	150–280
Plasma Fibrinogen (mg./100 ml. Mean and S.D.) ..	135–540 334 ± 51	130–680 324 ± 123	120–640 325 ± 120
Cryofibrinogen (mg./100 ml. Mean and S.D.) ..	0–72 19·6 ± 18	0–172 48·3 ± 50	7–160 77·4 ± 42
Urine fibrinolysis (Units/100 mg. of creatinine Mean and S.D.)	7–240 95 ± 63	7–120 62 ± 38	7–150 43 ± 31
β-Lipoprotein (mg./100 ml.) ..	348–648	364–624	416–636
α-Macroglobulin (mg./100 ml.)	246–404	246–728	316–408

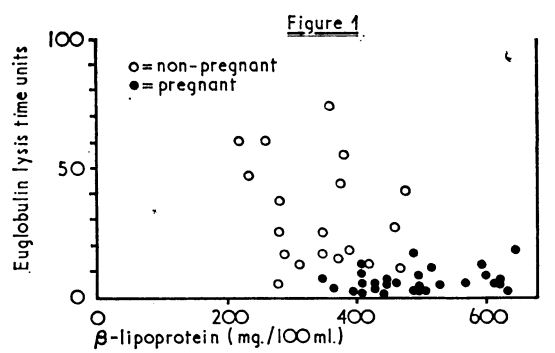
exceptionally high fibrinolytic activity for pregnancy but did not differ clinically from the other patients, and this was also the case in the minority of patients found to have high levels of inhibitors (though some of these had diabetes).

TABLE II.—*Number of Patients in Each Group*

	Euglobulin Lysis Time in Minutes			
	< 200	200–600	600–1,440	> 1,440
Normal	2	3	5	13
Hypertension	2	4	3	11
Toxaemia	0	1	11	11

	Plasma Inhibitors (Units)		
	< 40	40–100	> 100
Normal	2	18	3
Hypertension	0	18	2
Toxaemia	0	20	3

Levels of α_2-macroglobulin and β-lipoprotein were found to be raised in pregnancy (Table I), but again there was no significant difference among the clinical groups. No correlation could be shown at all between α_2-macroglobulin levels and the euglobulin lysis time or inhibitors as assayed, but in normal patients the lysis time was related to the levels of β-lipoprotein (Figs. 1 and 2).



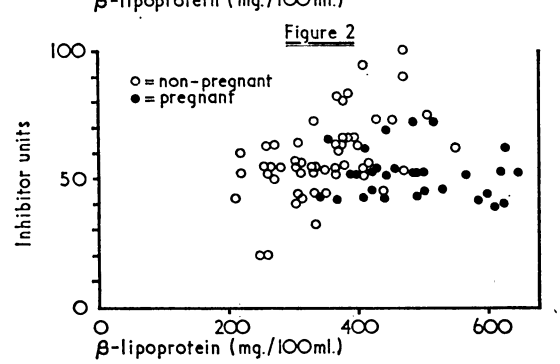


FIG. 1.—Relation between euglobulin lysis time and β-lipoprotein. ●=Non-pregnant. X=Pregnant. FIG. 2.—Relation between inhibitors and β-lipoprotein. ●=Non-pregnant. X=Pregnant.

Discussion

No difference has been found in fibrinolysis (as measured by the euglobulin lysis time) or in levels of fibrinolytic inhibitors between patients with pre-eclamptic toxaemia and those in late normal pregnancy. Hence to account for the appearance of fibrin in the glomeruli in toxaemia a low-grade intravascular coagulation must also be present as well as the considerable reduction of fibrinolysis. This suggestion is supported by the higher levels of cryofibrinogen in patients with toxaemia and hypertension compared with normal pregnancy, though plasma fibrinogen levels themselves are the same. It may be argued that thrombocytopenia should have been present if intravascular coagulation was taking place, but these were mild cases of toxaemia and no patients with eclampsia were seen.

We also found that urine fibrinolytic activity is reduced more in patients with hypertension and toxaemia. This may be a truer reflection of the fibrinolytic activity of the kidney.

Our findings are similar to those of Morris *et al.* (1964), who correlated biopsy findings with coagulation and fibrinolytic studies in patients with toxaemia. Those with abnormal biopsy findings had lower platelet counts, and, as a group, patients with toxaemia had greater prolongation of the euglobulin lysis time than had patients with normal pregnancy.

The "hypertensive" patients studied by us were those who showed a rise of blood pressure towards term but who had no oedema or proteinuria. Nevertheless, these patients were not true established hypertensives. Hypertension in pregnancy is known to carry an increased risk for mother and foetus (Tweedie and Mengert, 1965), and also the higher the blood pressure in pregnancy the more likely is a woman to have recurrent toxaemia. Some authors regard "toxaemia" without proteinuria as hypertension, and certainly recurrent toxaemia tends to pick out the potential or latent hypertensive (Chesley *et al.*, 1964), but it would seem that there is a spectrum of disease. In a follow-up biopsy study of toxaemia Smythe *et al.* (1967) showed that after the initial glomerular ischaemia due to endothelial swelling persistent glomerular changes occur in 10% of women and that 20% had true arteriolar disease six months after delivery. Moreover, the arteriolar changes were found to correlate better with the presence of clinical disease than did glomerular histology. Our findings here support a functional similarity between those patients with hypertension and those with proteinuria. In this connexion fibrinolysis is known to be reduced in simple benign hypertension (Prokopowicz *et al.*, 1967).

Reduced fibrinolytic activity in pregnancy has long been recognized. There is a reduction of release of plasminogen activator into the circulation (Shaper *et al.*, 1966 ; Nilsson and Kullander, 1967), and in addition there are inhibitors of both plasmin and plasminogen activator (Brakman, 1966) or urokinase (Shaper *et al.*, 1966) or both. Known serum inhibitors of fibrinolysis are α_2-macroglobulin (Ganrot, 1967), which has a high affinity for plasmin, α_1- and α_2-antitrypsin glycoproteins, which are present in high concentration (Gans and Tan, 1967 ; Niléhn and Ganrot, 1967), and β-lipoprotein. α_2-macroglobulin levels are raised in pregnancy (Schumacher and Schlumberger, 1963), and there are also raised levels of circulating triglycerides, of low-density lipoproteins, and of serum antitrypsin (Faarvang and Lauritsen, 1963). Urinary trypsin inhibitor excretion is also increased (Faarvang, 1959). Our results confirm that α_2-macroglobulin and β-lipoprotein levels are raised, but we have not found any significant difference among the clinical groups. We have not been able to show any correlation between α_2-macroglobulin level and the euglobulin lysis time or inhibitors as assayed, but the former is correlated with the β-lipoprotein levels (see Figs. 1 and 2), part of which are known to be included in the euglobulin fraction.

In part the discrepancies may be caused by the use of a combined direct assay for inhibitors of both plasminogen

activator and plasmin. Alternatively, plasmin inhibitors may always be present in serum in excess—especially if the plasmin levels are raised—so that a correlation between levels of individual globulins and euglobulin lysis time or inhibitors might not be expected.

It is possible to reconcile the various theories of the aetiology of toxaemia. Placental infarction is common and experimentally (Berger and Boucek, 1964) placental ischaemia will produce a toxaemia syndrome by the release of a vasoconstrictor humoral substance that was initially suspected to be renin or angiotensin. It can be postulated that the thromboplastin that is the basis of McKay's (1964) intravascular coagulation theory is also released from frank placental infarcts or from the degenerate trophoblast cells that are seen to be accompanied by focal fibrin deposits in the maternal spaces.

Sophian (1958) championed the theory that renal ischaemia is the direct result of uterine distension, and certainly a utero-renal vasoconstrictor reflex can occur, but the morphology of pre-eclampsia is different from that of acute or chronic renal ischaemia. In fact, the glomerular reaction and fibrin content could be the immediate cause of the low glomerular filtration rate and renal plasma flow, and indeed there is a good correlation between the histology of the kidney and the clinical and laboratory manifestations of toxaemia, such as a raised serum uric acid.

That toxaemia is increased when there is uterine distension —twins, hydramnios, hydrops foetalis, accidental haemorrhage —is accepted, but placental infarction and ischaemia may be more common in these circumstances. Changes in salt-and-water metabolism producing a syndrome akin to water intoxication can be the result of the renal morphological changes, as in acute nephritis. Recently it has been shown (Gordon *et al.*, 1969) that renin levels may be higher early in pregnancy in women who later develop toxaemia than in women in whom a normal pregnancy results ; renin may therefore not be directly responsible but may indicate a predisposition to placental ischaemia.

Fibrin can persist in renal glomeruli only when there is pronounced diminution of fibrinolysis, as is indeed the case in pregnancy. Much lower levels of fibrinolysis are seen in this physiological state than in many pathological conditions in which minor deviations of fibrinolysis are accorded a role. On the other hand, inhibition of fibrinolysis alone never causes fibrin deposition, for there must first be a trigger to the coagulation system. Our failure to find a difference in fibrinolysis between normal pregnancy and hypertension or toxaemia adds support to the thromboplastin release theory.

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Medical Research in the Caribbean

[FROM A SPECIAL CORRESPONDENT]

The 14th scientific meeting of the Standing Advisory Committee for Medical Research in the British Caribbean was held from 17 to 21 April on the St. Augustine Campus of the University of the West Indies, in Trinidad.

Most of the papers referred to present-day research by clinicians. Dr. P. E. B. RODGERS-CHRISTIAN (University of the West Indies) presented a paper on 50 cases of myasthenia gravis for which the incidence in Jamaica of 1 in 38,000 was higher than that reported elsewhere. In this condition there was a peak of onset in the second decade, which was lower than in other series, Thymectomy had given good results in 16 patients, one of whom had had a malignant thymoma. Professor J. W. SANDISON (University of the West Indies) examined the causes of death in 11 patients dying of moderate and severe tetanus (20% of the 56 cases seen since January 1965), and emphasized that in severe tetanus the mortality could be reduced to about 30% in centres where intensive care was available.

Diseases of the Cardiovascular System and Gut

Dr. W. E. MIALL (Medical Research Council Epidemiological Research Unit) had studied prognostic factors in heart disease, having re-examined 92% of 930 surviving patients aged 35–64 years in a rural area in Jamaica five years after their original examination ; 64 patients had died, and by using age-adjusted mortality ratios it was found that in either sex hypertension alone was not associated with a higher mortality than expected. Nevertheless, electrocardiographic evidence of ischaemia doubled the risk, and hypertension plus ischaemic changes trebled it. Angina was an important prognostic feature in both hypertensive and normotensive males.

Dr. M. T. ASHCROFT (M.R.C. Epidemiological Research Unit) had found prevalence of E.C.G. abnormalities in both East Indians