Clinicopathological spectrum of late postpartum renal failure: two contrasting cases

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SYNOPSIS The clinical and renal biopsy findings from two patients in whom renal functional abnormalities developed in the late postpartum period are described. Both biopsies showed fibrin deposition in the renal vasculature, in one case marked and in the other mild. The patient with the more severely damaged kidney subsequently died, and the other is alive but with evidence of slowly progressing renal damage. The clinicopathological spectrum and pathogenesis of late postpartum renal failure are discussed.

Acute renal failure as an immediate complication of parturition is well recognized. It is usually associated with a precipitating factor such as hypotension, haemorrhage, toxæmia, septicaemia or amniotic fluid embolism. It often involves an episode of disseminated intravascular coagulation (DIC) and in such cases may be referred to as the 'postpartum haemolytic uraemic syndrome'.

However, there is reported a distinct group of 29 patients developing acute renal failure following a spell, from 5 to 70 days, of good health after delivery. This group was first clearly defined by Robson *et al* (1968) and has been recently reviewed by Finkelstein *et al* (1974); additional cases are described by Smith *et al* (1965), Calvert (1972), and Williams and Hughes (1974). Most of these patients had absolutely normal pregnancies and none had more than mild pre-eclampsia. In no case was there an obvious precipitating factor for the renal failure but most showed evidence of DIC. The prognosis has been poor since only eight survived: three were chronic invalids (Robson *et al*, 1968; Ogg and Cameron, 1969); two had had bilateral nephrectomy (Erickson *et al*, 1971; Calvert, 1972); two had mild renal impairment and hypertension when reported (Luke *et al*, 1970; Ponticelli *et al*, 1970); and one (Finkelstein *et al*, 1974) was well and on no treatment. Renal histology, described in some detail in 24 patients, has been similar in all cases.

We report the clinical and biopsy findings from

two patients who developed acute renal failure, three and five weeks respectively, after normal pregnancy and delivery.

Case 1

This 24-year-old woman went through a completely normal third pregnancy and delivery. Twenty-six days postpartum she was admitted to hospital because of complete anuria for 36 hours. She had felt well for a week following delivery but then noticed swelling of the right side of the face and some abdominal distension. A week later she developed ankle swelling and for the week before admission she had been oliguric.

On examination she was found to have periorbital oedema and some bruises on the legs, and she was slightly pale. Jugular venous pressure was raised 2-3 cm above the sternum and the blood pressure was 140/80 mmHg. Fundal examination was normal.

Initial investigations showed haemoglobin 9.2 g/dl, WBC $8.9 \times 10^9/l$, and platelets $240 \times 10^9/l$. Blood film showed distortion of RBCs with marked schistocyte formation consistent with a microangiopathic haemolytic anaemia. Prothrombin time was 14 seconds (control 13 seconds), kaolin cephalin time 39 seconds (control 40 seconds), FDPs in blood 160 mg/l. Over the next few days the haemoglobin fell to 4.7 g/dl and platelets to $95 \times 10^9/l$. The reticulocyte count was 19.6% and schistocytes were numerous in the blood film. She was transfused 3 units of packed cells, and the haemoglobin remained in the 7-10 g/dl range until her discharge one month later with a haemoglobin of 9.5 g/dl, WBC $17 \times 10^9/l$, and platelets $200 \times 10^9/l$.

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Blood urea on admission was 43.7 mmol/l. This rose in four days to 49.8 mmol/l and was subsequently controlled by peritoneal dialysis. Initially, serum sodium was 136, potassium 4.5, and chloride 105 mmol/l.

A renal biopsy was performed two days after admission.

RENAL BIOPSY

Light Microscopy

Most glomeruli were damaged, the predominant abnormality being foci of intraglomerular capillary thrombosis (fig 1) and fibrinoid necrosis. In some glomeruli fibrinoid necrosis affected the root (fig 2) and was associated with a thrombosed and sometimes necrotic afferent arteriole—most afferent arterioles were thrombosed (fig 1). Glomeruli also showed swelling of endothelial cell cytoplasm, moderate proliferation of mesangial cells, and areas of increased mesangial matrix, while basement membranes did not show epimembranous spikes. Interlobular arteries showed slight intimal fibrous thickening and luminal narrowing. Tubules showed foci of atrophy and dilatation and contained numerous protein casts; interstitial tissue was not significantly abnormal.

Immunofluorescence Studies

These were carried out using fluorescein isothiocyanate-labelled rabbit antibodies to human fibrin-

ogen, IgA, IgG, IgM, and β_1C/β_1A globulin (Hoechst Pharmaceuticals). There was marked staining for fibrin in glomerular capillaries and afferent arterioles (fig 3). There was no staining for IgG or IgA, faint staining for β_1C/β_1A in glomerular capillary walls and some larger vessel walls, and diffuse staining for IgM in glomeruli and small vessels.

Electron Microscopy

There was obliteration of some glomerular capillaries by thrombi (fig 4) in which strands with appropriate periodicity for fibrin were identified; there was marked rarefaction of the endothelial side of the basement membrane but no deposits suggestive of immune complexes were seen. Some endothelial cells had a swollen pale cytoplasm. There was an increase in numbers of mesangial cells and matrix in some glomeruli with electron dense granular and fibrillar debris in mesangial regions. Fusion of foot processes was present in some areas.

SUBSEQUENT CLINICAL PROGRESS

On the basis of the clinical, haematological, and renal biopsy findings a diagnosis of late postpartum haemolytic uraemic syndrome was made and treatment with intravenous heparin was begun. Though haematological signs of DIC disappeared, there was no improvement in renal function, peritoneal

Fig 1 Case 1. The larger glomerulus contains a thrombus (arrowed) and shows a marked increase in mesangial cells. The smaller glomerulus is shrunk and rather solid, presumably due to ischaemia. Two cross sections of thrombosed arteriole lie below this glomerulus. Masson's Semichrome (MSB) $\times 310$.

Fig 2 Case 1. Fibrinoid necrosis at the root of the glomerulus (to left). There is also a marked increase in mesangial cells, an occasional neutrophil polymorph, and a thrombosed peripheral glomerular capillary. MSB $\times 325$.

Fig 3 Case 1. Immunofluorescence demonstration of fibrin in an afferent arteriole (bottom right) extending into the root of a glomerulus (upwards and left). $\times 935$.

and then haemodialysis being required. The patient was discharged from hospital one month after admission and attended weekly for haemodialysis. She remained reasonably well on ascorbic acid, 50

mg per day, Juvel, one tablet per day, folic acid, 5 mg per day, and Aludrox, 15 ml twice a day, for the next six months. Towards the end of this period she cooperated less well with the haemodialysis unit

Fig 4 Case 1. Electron micrograph of a thrombosed glomerular capillary. Foot processes of an epithelial cell are present at the top and on the right. The lumen of the capillary is full of debris in which several platelets and several strands (banded) of fibrin are present. $\times 12\,000$.

and then died suddenly and rather unexpectedly. Permission for necropsy was refused.

Case 2

This 35-year-old woman went through a completely normal fourth pregnancy and delivery. She was well for 15 days postpartum, then noticed ankle oedema for which a diuretic was given. On the 36th postpartum day she developed a headache and vomiting, and her face became puffy. That night she had a generalized convulsion and was admitted to hospital where she had a further fit.

Blood pressure on admission was 200/120 mmHg; she had mild generalized oedema and 'heavy' proteinuria. Haemoglobin was 14.7 g/dl with normochromic normocytic red cells, WBC $15.8 \times 10^9/l$ with a polymorphonuclear leucocytosis; platelets were reported as 'plentiful'. Serum bilirubin was 6.8 $\mu\text{mol/l}$, blood urea 10.6 mmol/l, electrolytes normal, serum albumin 26 g/l, and serum globulin

37 g/l. Mid-stream urine culture was sterile and antistreptolysin O titre less than 200 Todd units.

She was never oliguric and had no further fits. She was treated with diazepam, phenobarbitone, and frusemide; hypertension was first controlled with clonidine until methyldopa was substituted later. The blood urea fell to normal in three weeks, although the creatinine clearance then was only 40 ml/min (serum creatinine 177 $\mu\text{mol/l}$). Haemoglobin, WBC, platelets, and film were by now all normal and remained so. A week later excretion urography revealed no abnormalities in the kidneys or urinary tract; the fundi were normal, there was slight ankle oedema, proteinuria 2.5 g/day, and blood pressure 180/110 mmHg.

Eleven weeks postpartum a renal biopsy was taken.

RENAL BIOPSY

Light Microscopy

There were several extensively sclerosed glomeruli, and most others had rather focal proliferation of

mesangial cells and increased mesangial matrix (fig 5). All arterioles showed brightly eosinophilic hyaline walls, some staining red with MSB (Lendrum *et al*, 1962) suggesting the presence of fibrin, and had narrowed lumens (fig 5). Interlobular arteries showed marked luminal narrowing, in some vessels due to formation of concentric layers of cells, and in others due to irregularly arranged cells and hyaline material, probably old thrombi. There was patchy tubular atrophy, colloid casts in tubules, and a diffuse increase in interstitial tissue.

Immunofluorescence Studies (performed as for case 1)

There was fibrin in the lumens and walls of small vessels (fig 6) but only minimal deposits in glomeruli. No deposits of IgA, IgG, IgM or β_2 C/ β_2 A globulin were found.

Electron Microscopy

There were fibrils, some with a periodicity of 200 Å (close to that of fibrin), in patches along the endothelial side of the basement membrane, which appeared somewhat rarified (fig 7). No deposits suggestive of immune complexes were seen. There was an increase in mesangial cells and mesangial matrix. Fusion of foot processes was present in some areas.

SUBSEQUENT CLINICAL PROGRESS

The patient was discharged home 12 weeks postpartum, feeling well but requiring 1 g methyldopa and 10 mg bendrofluazide daily to control her blood pressure. Since leaving hospital she has remained well but has required continued therapy for hypertension. Now, 39 months after the onset of her illness, her blood urea is 14.9 mmol/l and creatinine clearance 28 ml/min.

A repeat renal biopsy was performed at 36 months.

REPEAT RENAL BIOPSY

Light Microscopy

The appearances were virtually indistinguishable from those of a late stage of benign essential hypertension: many glomeruli showed complete ischaemic obsolescence (fig 8) and others less advanced stigmata of ischaemia, such as thickening and wrinkling of capillary basement membranes with partial collapse of the tuft, in some instances associated with incipient intracapsular collagenization. The only evidence of previous proliferative activity was the presence of a few glomeruli showing focal or more diffuse sclerosis. Interlobular arteries and arterioles showed marked but variable hyaline thickening of walls (not staining as fibrin with MSB)

Fig 5 Case 2. The MSB stained glomerulus on the left shows an increase in mesangial cells and matrix of a rather focal nature. The afferent arteriole contains a lozenge of fibrin in its wall, and its lumen is markedly narrowed. The methenamine silver stained glomerulus on the right shows rather focal increased mesangial staining. Both $\times 260$.

Fig 6 Case 2. Immunofluorescence demonstration of fibrin in arteriolar wall (just below and left of centre) and lumen (just left of centre). Part of a glomerulus in the upper right part of the field shows virtually no fibrin staining. $\times 425$.

and narrowing of lumens. Tubules showed patchy but extensive atrophy.

Immunofluorescence Studies (performed as above)

No fibrin was seen and only a few scattered deposits of IgM in one severely damaged glomerulus. There were no glomeruli in the tissue submitted for electron microscopy.

Discussion

We believe that patients should be considered as belonging to the clinicopathological syndrome of 'late postpartum renal failure' only provided that (a) they have had a normal or near normal pregnancy and delivery, (b) they have had a period (arbitrarily more than 24 hours) of good health between delivery and the onset of renal failure, and (c) they develop symptoms within three months of delivery. Criteria (a) and (b) exclude patients with other well-recognized pregnancy-associated causes of renal failure and patients in whom renal failure is the result of an immediate complication of delivery. Criterion (c) seems desirable as three months is the usually accepted time required for complete uterine involution and return to non-pregnant physiology. This criterion would exclude

cases 3 and 4 of Churg *et al* (1970); these two patients did not develop symptoms until approximately 6 and 7½ months postpartum, and we have not included them in our count of 29 previously reported cases.

Although the aetiology of this syndrome remains unknown, the previous biopsy findings, particularly on light microscopy (Scheer and Jones, 1967; Robson *et al*, 1968; Wagoner *et al*, 1968; Clarkson *et al*, 1969; Ogg and Cameron, 1969; Rosenmann *et al*, 1969; Luke *et al*, 1970; Ponticelli *et al*, 1970; Erickson *et al*, 1971; Calvert, 1972; Eisinger, 1972; Massachusetts General Hospital, 1973; Finkelstein *et al*, 1974; Williams and Hughes, 1974), suggest that the renal damage is ischaemic in nature due to damage to and obstruction of small arteries and arterioles. These vessels regularly show fibrinoid necrosis, luminal thrombi, and intimal thickening, while glomerular changes, most commonly focal necrosis, are less consistent and presumably the result of ischaemia and fibrin deposition. Our patients' original light microscopic findings are similar to those of the other cases. The slowly progressing renal damage in the second patient appears to be the result of hypertensive vascular damage.

All reports of electron microscopy (Robson *et al*,

Fig 7 Case 2. Electron micrograph showing foot processes of an epithelial cell at the top and part of an endothelial cell at the bottom. The glomerular capillary basement membrane between contains fibrillar material (probably fibrin derived) in its rather rarified subendothelial part. $\times 40\,000$.

1968; Rosenmann *et al*, 1969; Finkelstein *et al*, 1974; Williams and Hughes, 1974) have noted material, fibrin-like or actually showing the periodicity of fibrin, in glomeruli and are in agreement with our findings. All six reports of immunofluorescence studies (Rosenmann *et al*, 1969; Ogg and Cameron, 1969; Ponticelli *et al*, 1970; Calvert, 1972; Massachusetts General Hospital, 1973; Williams and Hughes, 1974) have shown fibrin in glomeruli, three

have shown fibrin in arterioles (Rosenmann *et al*, 1969; Ponticelli *et al*, 1970; Massachusetts General Hospital, 1973), and only one details immune complex deposition (Rosenmann *et al*, 1969). Overall, these results hardly suggest an immune pathogenesis and are similar to ours.

THE ROLE OF DIC

Most recent authors regard the renal vascular

Fig 8 Case 2—second biopsy. An ischaemically obsolescent glomerulus. The shrunken solid PAS-positive tuft is surrounded by a mantle of PAS-negative collagenous material which fills the capsular space. PAS, Mayer's Lissamine Flavine $\times 320$.

damage and fibrin deposition as the result of an episode of DIC, and in fact the majority of reported cases have shown haematological evidence of this process. However, laboratory evidence of DIC is often transient, appropriate tests for its detection are often not done, or it may be so slight as to pass unnoticed (Flute, 1972). Consequently a lack of such evidence does not exclude DIC from a pathogenic role. In our first case, there is good haematological evidence of DIC, but in the second, the only relevant investigations done, namely, haemoglobin, blood film, and serum bilirubin, failed to show any evidence of DIC. Our reasons for considering that a relatively acute episode of intravascular fibrin deposition might have contributed to the renal damage in our second patient are: (a) The presentation with convulsions, hypertension, and established renal failure five weeks postpartum is suggestive of a widespread rapid onset disturbance of small blood vessels; (b) pre-existing renal disease is unlikely as the well-documented pregnancy and delivery were entirely normal; and (c) the biopsy findings (even though the biopsy was performed six weeks after the acute phase of the illness) are consistent with those reported from similar cases where there has been good evidence of DIC.

Neither of our patients nor any other reported cases of this syndrome had any of the disturbances,

such as sepsis or toxæmia, known to be capable of initiating intravascular coagulation, and the onset was too late to have been due to amniotic fluid embolism. It is of interest, therefore, to consider why DIC should occur in this particular group of women.

The normally delicate balance between coagulation and fibrinolysis within the vascular system is known to be altered in pregnancy with a rise in fibrinogen and factors V, VII, VIII, and X (Ulutin, 1969). At the same time some studies indicate a progressive decrease in fibrinolytic activity during pregnancy with, however, a rapid return to normal after delivery, while the levels of fibrinogen and factors VII and X return more slowly (Shaper *et al*, 1965). Thus, for some time following any normal delivery, the balance may be shifted in favour of coagulation. Most recent papers on late postpartum renal failure follow Clarkson *et al* (1969) and note the similarity between a generalized Shwartzman reaction and a catastrophic episode of DIC. They point out that, in pregnant animals, only one injection of endotoxin is necessary to precipitate the reaction instead of the usual two. This is ascribed to the reduced efficiency of the reticulo-endothelial system during pregnancy and its therefore reduced capacity to dispose of endotoxin and early products of intravascular coagulation, which themselves

promote further coagulation. Furthermore, results of a study of the effect of therapeutic abortions on coagulation and fibrinolysis suggest that delivery itself is a thromboplastic stimulus (Badraoui *et al*, 1973).

An additional factor possibly affecting the clotting system in this group of patients is drug administration. Ergot preparations are mentioned as having been given in 13 of the previous cases, were probably given in most of the others, and have never been reported as not given. Ergometrine administration in other parturient women has occasionally been followed by hypertensive crises lasting from a few hours to several days, sometimes accompanied by arteriolar spasm and thrombosis. Such crises occur shortly after administration of the drug; they are most likely to occur in toxæmic patients and where sympathomimetic vasoconstrictors have been used (Baillie, 1963). Our patients received Syntometrine (ergometrine 0.5 mg and oxytocin 5 units), but both were well for several weeks following its administration, were not toxæmic, and received no sympathomimetic drugs. Oxytocin, stated as given in five of the 31 previous cases but definitely 'not given' in some others, is not known to affect coagulation. Its use in much higher doses in other parturient women has been associated with transient oliguria, attributed to its antidiuretic hormone-type effect, and quick recovery has followed its withdrawal (Shipman *et al*, 1964).

Oestrogens, definitely given in six previous cases and our second case, have been shown in women to increase inhibitors of fibrinolysis (Phillips *et al*, 1961), the fibrinogen level (Phillips *et al*, 1961), and platelet adhesiveness (Bolton *et al*, 1968).

All the above conditions are, however, present in countless obstetric patients who never develop overt vascular damage, so there remains in our patients and the others no obvious precipitating factor.

Conclusion

The clinical and renal pathological findings in two patients with late postpartum renal failure are presented. The first patient, with severe renal damage due to DIC, lost all useful renal function as a result of her illness. The second, with milder renal damage, remains well although showing signs of slowly deteriorating renal function. We wonder if there is a group of women who suffer from a mild unrecognized form of this syndrome and who go on to develop hypertension and/or renal failure in later life. A check on blood pressure, blood urea, and electrolytes at postnatal follow-up would pick up such patients and permit early treatment to be established.

The exact pathogenesis of the syndrome remains obscure.

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