antibodies previously present in the 10 cotwins in the long term group had disappeared in all but two (fig 3); (*c*) impairment of glucose tolerance was seen in cotwins in the short term group but not in those in the long term group; and (*d*) a prospective study of 10 other cotwins of short term diabetics who had been discordant for more than 10 years showed an improvement in glucose tolerance over that time (Heaton *et al*, paper presented to the British Diabetic Association, Belfast, 1985).

We do not know what determines whether the damage to the islets will lead to complete destruction of the insulin secreting cells or to their recovery. If the destruction is an immune mediated process then it may be a question of the intensity of that process; it can hardly depend on genetic predisposition alone, as our results come from identical twin pairs.

If we could understand what limits the immune mediated damage in those twins in whom it had remitted we might learn how to arrest the process before it leads to diabetes.

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# Effect of pregnancy on moderate renal failure in reflux nephropathy

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## Abstract

**During a 10 year study of women with reflux nephropathy 20 women had plasma creatinine concentrations in the range 0·2-0·4 mmol/l (2·3-4·5 mg/100 ml). Six experienced pregnancies exceeding 12 weeks' gestation. Pregnancy was associated with rapid deterioration in function in all six, resulting in end stage renal failure in four women within two years after delivery despite adequate control of blood pressure. Of the 14 women who did not have a prolonged pregnancy, four had periods of uncontrolled hypertension, all of which were related to non-compliance or loss from follow up, or both. Uncontrolled hypertension was also associated with accelerated renal failure, and all four women progressed quickly to end stage renal failure. The remaining 10 women were observed for from five to 10 years; in all 10 renal function deteriorated slowly, and none reached end stage renal failure within seven years.**

**It is concluded that pregnancy in patients with reflux nephropathy and moderately severe renal failure has a deleterious effect on renal function.**

## Introduction

The effect of pregnancy on renal disease is controversial. Some reports suggest that it is deleterious, especially if renal function is already impaired.[1-5] Others have argued that the rapid decline in renal function seen in some patients reflects the clinical course of the underlying disease.[6-11] We have reported a high incidence of complications in gravidas with reflux nephropathy.[12] Since 1973 we have prospectively studied patients presenting with reflux nephropathy to determine the features associated with a poor prognosis. We now present our findings.

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## Patients and methods

During a prospective 10 year study of patients with reflux nephropathy six women with plasma creatinine concentrations of 0·2-0·4 mmol/l (2·3-4·5 mg/100 ml) experienced pregnancies exceeding 12 weeks' gestation. The course of renal disease during and after the pregnancy in these six patients was compared with that in 14 women with the same degree of renal impairment who did not experience prolonged pregnancy.

Reflux nephropathy was considered to be present if the patient had the typical radiological features of clubbed polar renal calices with overlying cortical scars.[13] In all but one vesicoureteral reflux had been shown at some time on micturating cystography. In 15 from whom renal biopsy tissue was available, including the one in whom reflux had not been documented, histological findings were typical.[14] Plasma creatinine and urea concentrations were determined by autoanalyser (Technikon SMAC).

## Results

Twenty women with reflux nephropathy had plasma creatinine concentrations in the range 0·2-0·4 mmol/l (2·3-4·5 mg/100 ml) in the 10 years 1973-83.

### PATIENTS WITH PROLONGED PREGNANCIES

Six patients (mean age 26·0 (range 21-39) years) experienced pregnancies exceeding 12 weeks (table). All had plasma creatinine concentrations exceeding 0·2 mmol/l (2·3 mg/100 ml) before 20 weeks' gestation. In one case the fetus died in utero at 22 weeks, and one woman was delivered at 30 weeks of a baby that died of hyaline membrane disease. In the remaining four cases the babies were delivered at 30-38 weeks' gestation; all four babies survived. Four patients were treated during pregnancy with plasma exchange, in two cases after intravenous heparin treatment.

Renal biopsy was performed during pregnancy in two cases and within one month after delivery in one. All specimens showed considerable focal

and segmental glomerular hyalinosis and sclerosis and pronounced hyperplasia of vascular intima. One of the specimens obtained during pregnancy also showed fibrinoid intraglomerular lesions. The changes of pronounced vascular intimal hyperplasia and fibrinoid intravascular lesions were not seen in 11 biopsy specimens from patients with controlled blood pressure who were not pregnant at the time.

The table and figure 1 show the course of renal function in these six patients. Pregnancy was associated with deterioration of renal function in all cases, and further rapid deterioration occurred post partum, even in two patients who had had fairly stable function for years previously. This deterioration occurred despite close attention to control of hypertension (diastolic blood pressure did not exceed 100 mm Hg) and salt and water balance and absence of urinary infection. Four of the six patients were in end stage renal failure within two years after delivery.

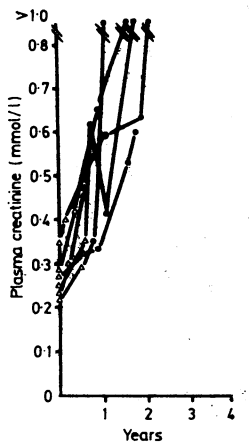


FIG 1—Course from early pregnancy in six patients with plasma creatinine concentration 0·2-0·4 mmol/l in first trimester of pregnancy lasting 20 weeks or more. △—△=Values during pregnancy. ●—●=Values post partum.
*Conversion: SI to traditional units*—Creatinine: 1 mmol/l≈11·3 mg/100 ml.

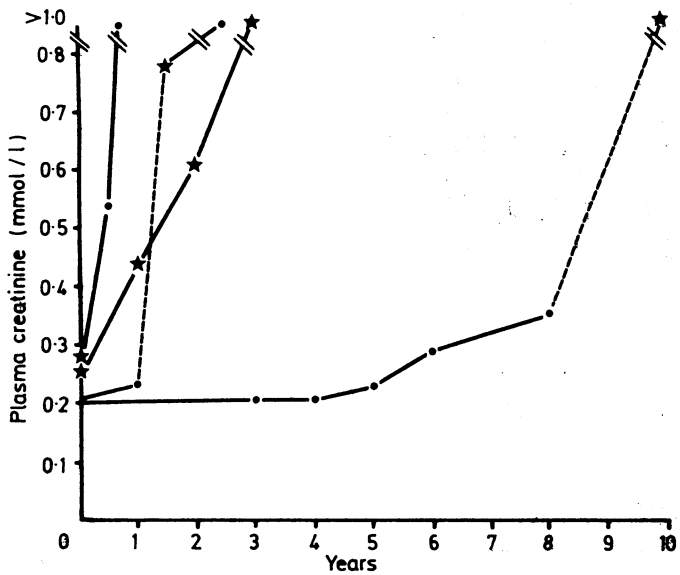


FIG 2—Course in patients with plasma creatinine concentration 0·2-0·4 mmol/l who experienced uncontrolled blood pressure (>120 mm Hg diastolic). (Graph begins at first recorded plasma creatinine concentration ≥0·2 mmol/l.) ——=Controlled blood pressure. ---=Lost to follow up. ★=Diastolic blood pressure >120 mm Hg.
*Conversion: SI to traditional units*—Creatinine: 1 mmol/l≈11·3 mg/100 ml.

### PATIENTS WITH ACCELERATED HYPERTENSION

Four patients (mean age 23·0 (range 17-23 years) had periods of accelerated hypertension associated with rapid decline in renal function (fig 2). Three had been lost to follow up for from six months to three and a half years before returning; two were in or near end stage renal failure. The third had been observed for 17 months with a stable plasma creatinine concentration of 0·13 mmol/l (1·5 mg/100 ml) before she was lost to follow up for three and a half years. Two years before representing she completed a pregnancy complicated by hypertension, and she was referred back to us with a plasma creatinine concentration of 0·29 mmol/l (3·3 mg/100 ml), a diastolic blood pressure of 130 mm Hg, and retinal haemorrhages. She rapidly progressed to end stage renal failure despite control of hypertension. The fourth patient was non-compliant and usually had a diastolic blood pressure exceeding 120 mm Hg.

### PATIENTS WITH CONTROLLED HYPERTENSION AND NO PREGNANCIES

Ten patients (mean age 29·4 (range 16-53) years) in whom neither pregnancy nor accelerated hypertension occurred showed slow deterioration of renal function (fig 3). All had hypertension controlled with antihypertensive drugs. In no case was the deterioration as rapid as that seen in the pregnant patients or those with accelerated hypertension.

## Discussion

In this study of women with reflux nephropathy and moderate renal failure renal function slowly deteriorated in 10 patients who did not experience prolonged pregnancy (>12 weeks) or uncontrolled hypertension. None of these patients reached end stage renal failure in less than seven years from the first time their plasma creatinine concentration reached 0·2 mmol/l or more (≥2·3 mg/100 ml). Renal function deteriorated rapidly in all six patients who experienced pregnancies exceeding 12 weeks' gestation and in four patients who had periods of accelerated hypertension. In the pregnant patients this deterioration occurred during pregnancy and post partum despite good control of blood pressure. Four of the six were in end stage renal failure within two years after delivery.

*Renal function and outcome of pregnancy in pregnant patients*

| Case No | Age at conception (years) | Initial follow up: Time before pregnancy | Initial follow up: Plasma creatinine (mmol/l) | Initial follow up: Urine protein (g/24 h) | Follow up during pregnancy: Gestation (weeks) | Follow up during pregnancy: Plasma creatinine (mmol/l) | Follow up during pregnancy: Urine protein (g/24 h) | Subsequent follow up: Time after delivery (months) | Subsequent follow up: Plasma creatinine (mmol/l) | Subsequent follow up: Urine protein (g/24 h) | Fetal outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 39 | | | | 16 | 0·24 | 1·4 | 8 | 1·21 | 3·2 | 850 g, died at 6 days |
| | | | | | 30 | 0·29 | 1·2 | | | | |
| 2 | 21 | 8 years | 0·10 | | 4 | 0·25 | 2·1 | 12 | 0·93 | 2·9 | 1090 g, survived |
| | | 3 years | 0·20 | | 30 | 0·29 | 2·0 | | | | |
| 3 | 21 | | | | 20 | 0·25 | | 12 | 1·8 | 2·5 | Survived |
| | | | | | 38 | 0·42 | 3·0 | | | | |
| 4 | 24 | | | | 20 | 0·35 | 1·4 | 23 | 1·0 | 2·7 | Death at 22 weeks |
| | | | | | 22 | 0·50 | 3·9 | | | | |
| 5 | 29 | 10 years | 0·14 | 4·0 | 8 | 0·26 | 1·2 | 6 | 0·60 | 2·0 | 1368 g, survived |
| | | 6 months | 0·27 | 1·2 | 30 | 0·31 | 1·3 | 12 | 0·88 | 2·2 | |
| | | | | | | | | 18 | 0·84 | 2·1 | |
| 6 | 21 | | | | 12 | 0·22 | 3·1 | 5 | 0·47 | | 1498 g, survived |
| | | | | | 30 | 0·34 | 5·2 | 12 | 0·52 | | |

*Conversion: SI to traditional units*—Creatinine: 1 mmol/l≈11·3 mg/100 ml.

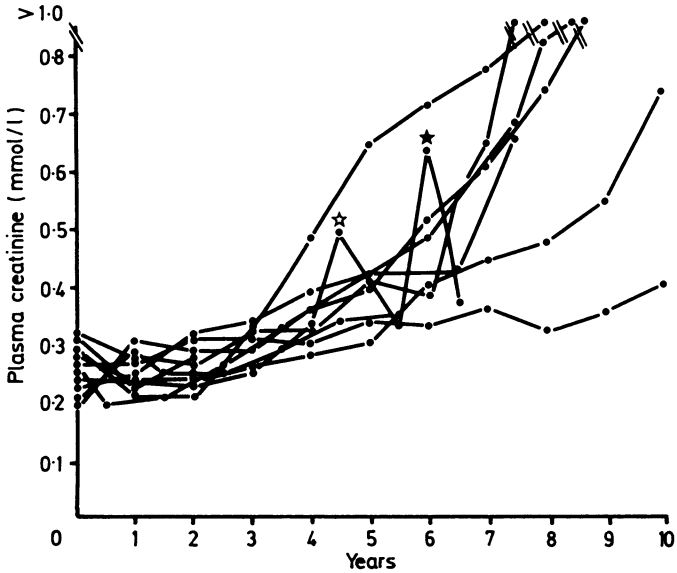


FIG 3—Course in patients with plasma creatinine concentration 0·2-0·4 mmol/l who did not experience prolonged pregnancy or uncontrolled blood pressure. (Graph begins at first recorded plasma creatinine ≥0·2 mmol/l.) ☆=Pregnancy to 12 weeks' gestation. ★=Uretic obstruction by calculus.

*Conversion: SI to traditional units*—Creatinine: 1 mmol/l≈11·3 mg/100 ml.

This poor prognosis in pregnant patients with reflux nephropathy and a plasma creatinine concentration greater than 0·2 mmol/l is similar to that in isolated patients reported on previously,[3 15 16] all three of whom were in or near end stage renal failure within 18 months after delivery. The normally slow progress of the disease in the absence of hypertension or pregnancy is consistent with findings in other series.[17 18] The cause of this decline in renal function related to pregnancy is uncertain, although several contributing lesions might be responsible. Worsening of vesicoureteral reflux by pregnancy is unlikely to contribute. Two of our six patients had undergone successful reimplantation of their ureters before their pregnancies. The fairly high blood pressures experienced intermittently during pregnancy may have contributed, but the diastolic pressure did not exceed 100 mm Hg.

We previously suggested that acute fibrinoid vascular lesions, such as those that occur in postpartum renal failure, may play a part.[19] Pregnancy accelerates focal and segmental glomerular hyalinosis and sclerosis in patients with glomerulonephritis.[19 20] All three patients who underwent renal biopsy showed evidence of this complication of reflux nephropathy, which is usually accompanied by increased proteinuria, hypertension, and deterioration in renal function.[14] One patient in this series showed acute intraglomerular fibrin thrombi during pregnancy, lesions that may well precede segmental hyalinosis. These lesions were not seen in patients who were not pregnant. Taylor *et al* suggested that pregnancy also has a similar deleterious effect in primary focal and segmental glomerular hyalinosis and sclerosis.[21] Recently it has been suggested that focal and segmental glomerular hyalinosis and sclerosis results from glomerular overload, or hyperfiltration,[22] a condition that could be worsened by the high glomerular filtration rate that persists throughout pregnancy. The mechanism by which hyperfiltration causes focal and segmental glomerular hyalinosis and sclerosis is unclear, although there is some evidence in animal models that drugs that inhibit intravascular coagulation can protect against focal and segmental glomerular hyalinosis and sclerosis.[23 24]

A similar deleterious effect of pregnancy in other diseases causing renal failure seems likely. We reviewed reported cases of pregnancy in patients with glomerular lesions and found that deterioration of function was almost universal if plasma creatinine concentrations exceeded 0·2 mmol/l in the first trimester.[25] Hou *et al* reported a series of 25 pregnancies in women with a plasma creatinine concentration ≥0·12 mmol/l (≥1·4 mg/100 ml) and found a dramatic decline in renal function in almost one third of these patients; three patients had a plasma creatinine concentration of ≥0·2 mmol/l, and all suffered a decline in renal function. As in our series the deterioration continued after delivery, a phenomenon of great importance. The mechanisms are likely to be similar.

The suggestion that intravascular thrombosis might play a part in the pathogenesis of the deterioration in renal function related to pregnancy led us to use antithrombotic agents such as antiplatelet drugs, heparin,[26] and, more recently, plasma exchange[27 28] in the treatment of such patients. Four of the current series of patients were treated with heparin or plasma exchange, or both, and three delivered live babies.[28] The aggressive treatment during pregnancy did not prevent rapid postpartum deterioration in renal function. In fact, by prolonging the pregnancy it may have worsened the maternal prognosis. In four patients plasma exchange was continued for between two weeks and three months post partum. Renal function partially stabilised during this time in three patients but deteriorated subsequently.

We believe that women with reflux nephropathy and impaired renal function (plasma creatinine concentration >0·2 mmol/l) should be warned that end stage renal failure is likely to occur as a result of pregnancy.

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