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Pregnancy and the Nephrotic Syndrome

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Summary: Nineteen patients with nephrotic syndrome, 13 with histological diagnosis, were studied throughout 31 pregnancies. Eight were diagnosed for the first time during pregnancy.

Antenatal problems due to severe oedema, urinary tract infection, and refractory orthochromic anaemia were encountered. Eight patients were hypertensive at booking, and in two of these pregnancy was terminated; three others had a significant increase in blood pressure. In 12 of the remaining pregnancies a rise in blood pressure of 20 mm. Hg or more occurred towards term.

There were 29 live births (including one set of twins), one stillbirth due to a cord accident, and one neonatal death. The infant birth weight, apart from being affected by hypertension, was related to the maternal serum albumin level.

The patients have been under observation for up to 20 years. Fifteen have not shown any deterioration of renal function during the prolonged period of observation. One developed oliguric renal failure immediately post partum and three others died, two, four, and 12 years after their pregnancies.

Introduction

The relationship between pre-eclampsia and the nephrotic syndrome has remained confused and poorly understood, largely owing to the varied morbidity and clinical course of both conditions. Without renal biopsy or long-term clinical studies the distinction may be extremely difficult. This similarity has led to the misdiagnosis and underreporting of the coexistence of nephrotic syndrome with pregnancy, estimated by Wegner (1937) as occurring in 0.028% of pregnancies. The nephrotic syndrome has been claimed to result from severe pre-eclampsia (Hopper *et al.*, 1961; Sarles *et al.*, 1964), and cyclical nephrotic syndrome has been reported as occurring only during pregnancy (Schreiner, 1963).

The established view of Dieckmann (1936) and Wegner (1937) that pregnancy had a deleterious effect on chronic renal disease has been challenged by Seftel and Schewitz (1957), Silberman and Adams (1962), Marcus (1963), and Johnston *et al.* (1963), who have stressed the good maternal prognosis during pregnancy and the low rate of foetal loss. This communication is a study of 31 pregnancies occurring in 19 patients with the nephrotic syndrome. Many of these patients have been under careful long-term surveillance for more than 10 years. These pregnancies can therefore be viewed as isolated occurrences against the natural history and pathology of the renal disease, thus correcting the lack of long-term follow-up available in previous publications.

The cases have been selected by rigid biochemical criteria (Squire *et al.*, 1957), all having had at some time a serum albumin of less than 2 g./100 ml. and a proteinuria of more than 5 g./day. In eight patients (Table I) the nephrotic syndrome was first diagnosed during pregnancy, though in two of these there was a past history of previous acute renal disease. In the remaining 11 patients (Table II) renal disease had been present from 1 to 15 years before the pregnancies studied. Five patients in this group were receiving steroid therapy throughout eight pregnancies and two others had already completed successful courses of steroids before the onset of their three pregnancies. Two of these patients (Cases 10 and 11) and one patient (Case 18) who exhibited a progressive spontaneous recovery after the first pregnancy were the only patients who did not show severe clinical and biochemical evidence of the nephrotic syndrome at the time of the pregnancies. Two pregnancies were terminated at 16 weeks by hysterotomy on account of increasing oedema and hypertension. Apart from the 31 pregnancies in the present study, there were two spontaneous abortions without biochemical data.

Histological Diagnosis

Renal biopsy was performed before or after pregnancy in 13 cases. Case 5 had a second biopsy one year after the pregnancy and Case 2 had two renal biopsies following the initial biopsy taken at the time of caesarean section. The staining techniques and criteria of histological diagnosis were those used by Brewer (1964). The clinical history and progress, bio-

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TABLE I.—*Nephrotic Syndrome Presenting During Pregnancy*

Case No.	Pathology	Date of Pregnancy	B.P. at Booking	B.P. in Late Pregnancy	S. Alb. (g./100 ml.)	Urea (mg./100 ml.)	Maturity in Weeks	Onset	Weight (g.)	Creatinine Clearance in 1968 (ml./min.)
1	Membranous	1959	130/90	150/100	2.5	15	36	Spontaneous	1913 2055	Died 1963 malignant hypertension
2	Membranous	1958	130/80	190/120	1.8	61	33	C.S. + steril.	1,700	80
3	Membranous	1955 1959 1966	140/80 140/80 160/90	150/100 150/100 200/120	N.K. 1.6 2.4	24 28 14	38 37 37	Induced Induced Induced	3,515 2,098 2,720	86
4	?Membranous	1964 1966	120/70 120/80	120/70 110/70	1.4 1.3	20 30	37 40	C.S. Induced	2,580 2,891	88
5	Proliferative	1962	N.K.	140/90	N.K.	40	40	Spontaneous	2,750	Died 1964 renal failure
6*	Proliferative	1967	120/80	200/110	0.9	110	33	Spontaneous	1,633	Anuric-chronic dialysis
7	?Proliferative	1964	120/80	140/80	1.9	30	40	Induced	2,820	56
8	—	1967	140/90	120/70	2.2	28	38	Induced	3,136	102

* Case 6 received steroid therapy for a trial period of 4 weeks during the pregnancy.

TABLE II.—*Pregnancies in Patients with Diagnosed Nephrotic Syndrome*

Case No.	Onset	Pathology	Creatinine Clearance	B.P.	Date of Pregnancy	B.P. in Late Pregnancy	Urea (mg./100 ml.)	S. Alb. (g./100 ml.)	Maturity in Weeks	Onset	Weight (g.)	Creatinine Clearance in 1968 (ml./min.)
			(Before Pregnancy)									
9	1960	Minimal change	117	110/70	1961* 1964*	110/70 110/70	33 20	2.0 4.2	37 40	Induced Induced	1,928 3,175	162
10	1960	Minimal change	71	110/60 110/70	1966† 1967†	110/70 100/60	30 24	3.9 3.8	40 40	Spontaneous Spontaneous	3,544 3,298	77
11	1958	Minimal change	142	130/85	1960†	130/80	15	4.0	40	Spontaneous	4,054	127
12	1959	? Minimal change	65	130/80	1966*	160/100	68	1.4	37	Induced	2,495	59
13	1953	Membranous	62	160/100 130/70	1961 1965	180/110 150/100	N.K. 30	N.K. 2.3	16 34	Terminated C.S. + steril.	— 2,210	142
14	1950	Membranous	23	250/150	1952	210/130	N.K.	N.K.	16	Terminated	—	Died 1964
15	1952	Membranous	108	160/100 150/100	1960* 1966	180/100 130/90	50 28	1.9 3.4	36 36	C.S. C.S. + steril.	2,735 2,976	105
16	1956	Proliferative	94	110/70 130/90	1963* 1965*	150/100 190/110	16 11	1.9 1.7	40 35	Spontaneous Induced	3,118 1,475	83
17	1957	Proliferative	80	140/90 190/95	1963* 1965*	150/100 190/110	24 26	2.1 2.9	38 33	C.S. C.S.	2,778 1,360	88
18	1952	—	N.K.	120/80	1955 1958 1960 1963	120/80 140/90 150/90 130/90	18 35 20 13	2.1 4.0 3.8 4.0	40 40 40 39	Spontaneous Spontaneous Spontaneous Spontaneous	3,298 3,204 3,714 3,288	180
19	1933	—	N.K.	120/70	1947	130/70	28	2.6	37	C.S. + steril.	2,608	60

* Steroids administered during pregnancy. † Completed successful steroid course before pregnancies.

chemistry, and differential protein clearances as described by Blainey *et al.* (1960) enabled a fairly confident diagnosis to be made in three cases without renal biopsy (Table III). Three further cases, also without biopsy, were of an undetermined type of glomerulonephritis. Kark *et al.* (1958) described the many renal lesions that may produce the nephrotic syndrome in adults, but only patients with the basic pathology of glomerulonephritis were encountered in this series.

TABLE III

Diagnosis by	Biopsy	Protein Clearances	
Minimal change glomerulonephritis ..	3	1	
Proliferative glomerulonephritis ..	4	1	
Membranous glomerulonephritis ..	6	1	
Undetermined type	—	—	3

Biochemical Changes During Pregnancy

Data concerning the quantity of proteinuria during pregnancy are often inadequate, sometimes unrecorded, or expressed as + + +, or by the grossly inaccurate Esbach technique. Urinary protein loss was estimated serially in the four most recent patients who had a gradual and variable increase in proteinuria in the first half of pregnancy. There did not seem to be a further increase towards term or with the advent of hypertension. In Case 9 massive increases in proteinuria

occurred on two occasions when an attempt was made to lower the steroid dose, but with a return to 60 mg. of prednisolone daily the pregnancy was able to continue for 37 weeks with protein loss of only 2 g./day. The quantity of proteinuria usually decreased markedly in the puerperium and was followed by a diuresis and a considerable loss in weight.

The lowest serum albumin levels observed during each pregnancy are recorded in Tables I and II. The oedema was pronounced in all patients, except during the seven pregnancies that occurred when the renal disease was in remission and in the second pregnancy in Case 9, when the renal lesion was being successfully treated with steroids. Three patients developed severe vulval oedema: Case 2 had a caesarean section at 33 weeks and has subsequently made virtually a complete spontaneous recovery; Case 12 required intravenous infusion of albumin as well as the more usual treatment of high-protein and low-salt diet, diuretics, and steroids, and had a successful pregnancy. The other (Case 6) is described in full below.

Clinical Manifestations During Pregnancy

Refractory orthochromic anaemia of less than 10 g./100 ml. occurred in 11 pregnancies, including one set of twins.

The blood pressure at the booking clinic was compared with that obtained during the week preceding delivery. In eight pregnancies a blood pressure of 140/90 or higher was recorded,

in three of these the systolic or diastolic pressure had increased by at least 20 mm. Hg towards term, and two cases (Nos. 13 and 14) with severe hypertension were terminated soon after their initial antenatal visit. Twenty-two pregnancies were normotensive at booking; 12 of these showed similar significant increases in blood pressure in the final weeks of pregnancy. The remaining patient (Case 5) was first seen in labour with a blood pressure of 140/90.

A urinary tract infection occurred in 11 pregnancies, in one patient producing a transient rise in blood urea to 90 mg./100 ml. One patient suffered from a chronic paronychia and boils. Five of these 11 patients were undergoing steroid therapy at the time, and one of this steroid group was admitted in her second pregnancy with bronchopneumonia as well as a recurrent urinary infection. There were no cases of severe infection in the puerperium.

There were 29 live births and one stillbirth. Labour occurred spontaneously from 33 to 40 weeks in 11 pregnancies. Fifteen were induced or underwent caesarean section before term. Three pregnancies were induced at term. No pregnancy was allowed to become postmature. In all, 11 pregnancies went to term. The stillbirth was caused by a cord around the neck at birth after the foetal heart had been clearly heard during labour. One infant delivered abdominally at 33 weeks was noted to be oedematous and died after two days.

The birth weights and gestational ages of the 30 infants documented in Tables I and II are expressed in Table IV as percentiles from the charts of Lubchenco *et al.* (1963).

TABLE IV

Percentile:	10	25	50	75	90	90+
B.P. > 140/90 ..	3	4	4	1	2	—
B.P. < 140/90 ..	1	2	4	6	—	1
Total ..	4	6	8	7	2	1

One set of twins of 10 and 25 percentile birth weight are not included. It is noteworthy that four of the singleton infants were dysmature, taking the 10th percentile as a definition, and the overall pattern is one of infants of slightly less than average birth weight, with a preponderance of small babies born to hypertensive mothers. The four infants from mothers in a recovered phase of the nephrotic syndrome were all above average size, whereas the infants of the hypoalbuminaemic (Cases 4, 7, and 9) even in the absence of maternal hypertension, were below the 25 percentile. Fig. 1 shows that in 26 pregnancies the foetal birth weight was clearly related to the level of serum albumin in the mother.

FIG. 1.—Association of low foetal birthweight with severity of maternal hypoalbuminaemia during pregnancy.

Five patients had eight pregnancies while being treated with steroids. Two of these patients in three pregnancies were delivered by caesarean section and the remainder per vaginam. There were no congenital abnormalities, but two infants of hypertensive mothers were below the 10th percentile.

Puerperium

No patient had any thromboembolic problem, though the suggestion of Marcus (1963), that patients with the nephrotic syndrome have a tendency towards hypercoagulation states in pregnancy and the puerperium, persuaded us to anticoagulate the three most recent patients.

Most patients underwent a heavy diuresis in the first postpartum week, the weight of the oedematous patients falling by as much as 10 kg. in that time. The failure of diuresis in Case 6 was unexpected and heralded the onset of oliguric renal failure.

Long-term Follow-up of Renal Conditions

Six patients (two on steroids) showed a marked improvement of renal function following the pregnancy. One of this group spontaneously improved through all of three pregnancies, and had no proteinuria in her fourth pregnancy. Another patient, with a diagnosis of membranous glomerulonephritis discovered during pregnancy, had an elective caesarean section and tubal ligation at 33 weeks for increasing oedema and nitrogen retention, and has made an almost complete spontaneous recovery over the course of 10 years with proteinuria of 1 g./day, normal renal function, and a biopsy picture of lobular basement membrane thickening.

Only in Case 6 (see Fig. 2) was there obvious deterioration of renal function during pregnancy.

FIG. 2.—Further data on Case 6. Patient with nephrotic syndrome diagnosed for the first time during the pregnancy which resulted in oliguric renal failure.

Case 6.—A 26-year-old primigravida had no symptoms of renal disease when she first attended the antenatal clinic at 14 weeks' gestation. She gave a history of acute glomerulonephritis and rheumatic fever when 10 years old, remaining well when follow-up was discontinued five years later. She had a blood pressure of 140/90 mm. Hg and a proteinuria of 7 g./day. Ankle oedema occurred at the twenty-first week of pregnancy, becoming more severe with increasing maturity despite high-protein and low-salt diet, rest, and diuretics. She was admitted with severe vulval

oedema 10 days later, her weight having increased by 16 kg. since the first antenatal clinic visit. The mild hypertension of 140/95 was treated with 1 g. of methyldopa daily. She was given two units of whole blood. Prednisone 20 mg. daily did not decrease the quantity of the unselective proteinuria and was discontinued after four weeks. Bed rest, dietary control, and alternate courses of chlorothiazide and spironolactone did not produce a diuresis. Other data are given in Table V. She remained normotensive and the oedema persisted. She was allowed home for a short time, to be readmitted in spontaneous labour 10 days later, at 33 weeks' maturity. Her blood pressure was 200/110. Haemoglobin concentration of 6.8 g./100 ml. was corrected during labour with packed cells. She had a normal vertex delivery of a premature infant weighing 1,633 g. The placenta was retained and the blood loss during labour of 1 litre was replaced. Post-partum diuresis did not occur and peritoneal dialysis was begun on the twelfth post-partum day. Renal venography excluded a renal vein thrombosis. L.E. cells were not found. Renal biopsy showed a severe proliferative glomerulonephritis with organizing epithelial crescents. The patient was accepted for chronic dialysis and at the time of writing was dialysed three times a week at home. Nine months after delivery she was normotensive with a urinary volume of 50 ml./day and proteinuria 1 g./day.

TABLE V

Maturity in Weeks:	14	26
Serum creatinine (mg./100 ml.)	1.0	2.25
Serum albumin (g./100 ml.)	2.0	0.86
Haemoglobin (g./100 ml.)	11.9	10.2
Complement (units/ml.) (normal 35 ± 5) ..	13	11

One of the two patients terminated at 16 weeks as a result of increasing oedema and hypertension died of renal failure and malignant hypertension 12 years later; the other termination was followed by a successful pregnancy four years later. Her renal function and blood pressure continued to improve. One patient (Case 1) with membranous glomerulonephritis and one (Case 5) with proliferative glomerulonephritis died of renal failure two and four years after their pregnancies respectively. Though the death in Case 5 was hastened by poor social conditions and self-neglect, it is believed that the deterioration in these patients represented the expected deterioration of the chronic renal disease.

Ten patients reviewed after from 1 to 10 years have shown no progression of their renal disease following pregnancy, though one has hypertension. The only patient followed for 20 years has shown a gradual deterioration with moderate hypertension consistent with the expected natural history of the disease.

Discussion

The satisfactory result of pregnancy and long-term follow-up in the cases reviewed endorse our view that, with adequate supervision, the majority of patients with nephrotic syndrome pass through pregnancy without great danger. The data do not reproduce the experience of Kincaid-Smith *et al.* (1967), who found that one patient died of renal failure shortly after she had developed a severe nephrotic syndrome in early pregnancy, another required a renal graft, serial renal biopsies showing a considerable increase in the severity of the renal lesions, and five other patients with nephrotic syndrome showed "definite impairment of renal function persisting after pregnancy." Though 1 of the 19 patients in the present series developed renal failure, it is not possible to indict pregnancy for this deterioration. Rapid worsening does occur in the non-pregnant state, and renal biopsy in this case showed long-standing proliferative glomerulonephritis with crescent formation. There were no characteristic arteriolar thromboses that Robson *et al.* (1968) described in four cases of post-partum renal failure. Apart from her hypertension, uncontrolled latterly by large doses of antihypertensives, she had laboratory signs of activity of the renal disease—for example, rising blood urea which we ascribed to her high-protein diet, low comple-

ment, and grossly increased red and white cell excretion in the urine.

McKay (1963), in an account of 142 patients with chronic renal disease, including eight nephrotics, stated that there is rarely an indication for termination, even if the proteinuria is heavy, but in the presence of hypertension he suggested a "trial of pregnancy" with recourse to termination if renal impairment or hypertension becomes more severe. This has much to commend it if criteria of activity can be established. Increasing blood pressure, urinary red cell excretion, and a low serum complement are of bad omen, but a moderate rise of blood urea may result from the necessary high-protein diet or an acute urinary tract infection. The oedema, of multifactorial causation, is more dependent on changes in serum albumin and body sodium due to normal pregnancy adaptations than to glomerular fibrosis and destruction. Alarming as gross oedema may appear, therefore, it is not considered evidence of deterioration if it is not associated with nitrogen retention or hypertension and is to some extent responsive to the diuretics and raised protein diet.

Browne and Browne (1960) and Kincaid-Smith *et al.* (1967) suggested that the development of pre-eclampsia is a strong case for termination. Hypertension in these complicated pregnancies may be pre-eclampsia, but this is usually an impossible clinical diagnosis to make in the presence of renal disease, itself manifested by oedema, hypertension, and proteinuria, the usual signs of pre-eclampsia. This may be just a question of semantics, as we also believe that uncontrolled "hypertension of pregnancy" can only do harm to a damaged kidney.

Anaemia can be severe and must add to any placental insufficiency present. Retained placenta and post-partum haemorrhage will be tolerated badly by patients who are both anaemic and hypovolaemic, owing to the abnormal distribution of body fluids. Infection, being attributed to hypogammaglobulinaemia (Fishberg, 1954), can be troublesome in pregnancy and the puerperium. Urinary cultures must be performed frequently during the antenatal course, and Barnes (1965) recommended prophylactic antibiotics during labour. Unlike Wegner (1937) or Seftel and Schewitz (1957), who have reported post-partum sepsis, there were no cases of severe infection in the puerperium.

The range of infant birth weight was below average, particularly affected by hypertension. Hytten and Paintin (1963) showed that foetal birth weight is largely proportional to the normal increase in circulatory blood volume; it would appear that the decreased blood volume in severe pre-eclampsia and nephrotic syndrome may also be a factor in the causation of the small-for-dates baby. The association of low birth weight with a severe depletion of serum albumin in this study supports this observation. The decision to induce labour in cases of placental insufficiency associated with massive proteinuria is more difficult than usual, as one is denied the aid of assessment by urinary oestriol, which is unfortunately removed in a large and variable proportion with the protein before the oestriol assay is made.

We wish to express our thanks to our obstetric colleagues in the Midlands for allowing us to publish data concerning patients under their care and to Professor D. B. Brewer for his studies of the renal biopsies.

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Awareness during Caesarean Section under General Anaesthesia

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Summary: Investigation of a series of 150 obstetric patients, the majority undergoing caesarean section, showed the expected figure of 2% with factual recall. There was, however, a 17.3% occurrence of unpleasant recall—associated in 10 cases (6.6% of the total) with recall of pain. There was a negative correlation between the giving of a narcotic within six hours of the operation and the occurrence of unpleasant recall. Several other aetiological factors—age, parity, preoperative emotional tension, ventilation, nitrous oxide wash-out with oxygen, and nitrous oxide concentration—were investigated and no relation was found between them and unpleasant recall. It is suggested, therefore, that premedication still has an important function in light anaesthesia, using muscle relaxants, to prevent any form of unpleasant operative awareness.

Introduction

The problem of awareness during operation has been with us since the beginning of anaesthesia, and has been accentuated during the past 25 years, following the introduction of muscle relaxants combined with light anaesthesia (Parkhouse, 1960; *Lancet*, 1968). This paper presents a prospective study of these problems and suggestions for prevention and further study.

Method

The patients studied were those considered to be especially at risk of being aware because of light anaesthesia and lack of sedation—namely, obstetric patients anaesthetized at or near term in the Royal Infirmary of Edinburgh. The anaesthetists varied from consultants to registrars, but their technique was fairly standardized, being similar to that described by Hamer Hodges *et al.* (1959).

A cyclostyled form was completed by each anaesthetist, giving details of preoperative emotional state, premedication including sedation given during labour, anaesthetic drugs and dosage, gas flows and concentration of inhalational agents when used, the duration of nitrous oxide wash-out if performed, and any variation on the basic technique such as the administration of intravenous analgesics.

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During the operation any evidence of awareness was recorded in the three periods (a) before delivery, (b) during nitrous oxide wash-out, and (c) after delivery of the child. The criteria used to assess possible awareness were opening of the eyes and limb movements.

The degree of recovery from anaesthesia on leaving the theatre was noted and the patient was then visited twice—on the first occasion within a few hours of the anaesthetic, and secondly within 36 hours. The first visit was usually carried out by the administering anaesthetist and the second by one of us. At both interviews the same questionnaire was used—namely: (1) What was the last thing you remember before going to sleep? (2) What was the next thing you were aware of? (3) Did you dream? (4) Did you feel any pain before you woke up? (5) When did you first feel pain? (6) Would you object to a similar anaesthetic again?

The second interview was more searching and was used to separate recall of true dreams from the vague recollections of the immediate post-anaesthetic period.

In all cases where the recollection suggested factual recall, the patient's story was carefully compared with that of the obstetrician and with that of the anaesthetist present during the anaesthetic.

Results

A total of 150 unselected cases were investigated in the manner described. Three patients recalled facts from the anaesthetic period, and 46 recalled some form of dream sequence. Ten patients experienced pain during anaesthesia, two of these also had factual recall, while seven had dreams.

TABLE I.—Occurrence of Fact, Pain, and Dream Recall in 150 Patients

Operation	Occurrences					Patients		
	Fact Recall A	Pain Recall B	Dreams		Total Recall A+B+C+D	All Types Recall	No Recall	Total
			Pleasant C	Unpleasant D				
Sections:								
Elective ..	3	7	12	12	34	26	35	61
Emergency ..	0	3	8	10	21	19	56	75
Forceps ..	0	0	0	1	1	1	7	8
Tubal ligation ..	0	0	3	0	3	3	2	5
Manual removal	0	0	0	0	0	0	1	1
Total ..	3	10	23	23	59	49	101	150