SEMINARS IN
NEPHROLOGY

Thin Basement Membrane Nephropathy in Pregnancy

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There are several published series of pregnancy in patients with nonimmunoglobulin A mesangial proliferative glomerulonephritis (most of whom have thin basement membrane nephropathy [TBMN]). The aim of the present study was to review the maternal and fetal outcomes of pregnancy in women with TBMN. The medical and obstetric histories of 86 women with TBMN and their 182 pregnancies (one twin) were reviewed. Data were collected retrospectively in 164 pregnancies (90%) and prospectively in 18 pregnancies (10%). Hypertension (alone or with proteinuria) developed in 15 unmonitored pregnancies (9%), and proteinuria alone developed in the third trimester in 2 pregnancies (1%). Hypertension was more common in the prospectively monitored pregnancies (6 pregnancies, 33%). In all, there were 174 live births (95%), and all fetal deaths occurred in the first and second trimesters in the absence of maternal complications. However, all the mothers of the 4 small for gestational age babies had been hypertensive.

In TBMN, maternal hypertension, prematurity, and small for gestational age rates did not exceed those in the normal population. Overall, pregnancy in women with TBMN does not appear to be attended by a significantly increased maternal or fetal risk.

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During the 1980s and early 1990s, several large series describing the outcome of pregnancy in women with preexisting renal disease were published.[1-6] Fetal outcome, maternal complications during pregnancy, and, most contentiously of all, the possible deleterious effect of pregnancy on the natural history of the renal disease all were examined. A recent meta-analysis of these series[7] concluded there was an excess fetal mortality and maternal morbidity in pregnancy in primary renal disease and this risk varied for different histologic diagnoses. The investigators explained this by the associated risk factors of impaired renal function, preexisting hypertension, and nephrotic range proteinuria present at conception or early in pregnancy. They contended that the underlying type of renal disease did not, in itself, influence pregnancy outcome.

However, these and other investigators have failed to take into account the confounding effect of the mode of presentation of the patients included in the different series. That is, patients presenting as a result of the complications of pregnancy are likely to have a worse fetal and maternal outcome than is seen in pregnancies undertaken after the renal disease has been diagnosed. This has been our experience[6] and that of others.[3] If the natural history of a common primary renal condition is benign, then an analysis of a series with a high percentage of women presenting as a result of complicated pregnancies may bias toward predicting an unfavorable pregnancy outcome for all women with that disease.

Thin basement membrane nephropathy (TBMN) is an inherited condition affecting the kidneys that is present from birth and is accepted widely as having a benign prognosis.[8] It provides a clearly defined subgroup of patients with a primary renal condition in whom it is possible to assess pregnancy outcome and subsequently compare this with that in other primary renal diseases. This article describes a single nephrologist's experience over 12 years of managing the pregnancies of women with TBMN.

Methods

The clinical records of all parous women with TBMN who presented between 1991 and 2004 to a nephrologist with an interest in managing pregnancy were reviewed.

Patients were diagnosed as having TBMN on the basis of clinical features (isolated glomerular hematuria with a documented first-degree relative with hematuria) or renal biopsy

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Table 1 Biochemical and Urinary Data at Presentation for 86 Women With TBMN

	Mean	SD
Glomerular red blood cells	188	± 215 × 10^3/mL
Plasma creatinine	0.06	± 0.01 mmol/L
Creatinine clearance	1.85	± 0.64 mL/s
24-h urinary protein	0.14	± 0.19 g/24 h

examination findings (uniform basement membrane thinning on electron microscopic examination without superadded glomerular or interstitial abnormalities on light microscopy or immunofluorescence).

The patients' age and blood pressure measurements at presentation were noted. Patients were considered hypertensive if the diastolic blood pressure exceeded 95 mm Hg or if they already were taking antihypertensive agents. Each patient provided a midstream urine specimen that was examined by phase-contrast microscopy by an experienced observer and initial glomerular red blood cell counts were counted on an unspun sample. Biochemical data recorded on each patient included serum creatinine level (mmol/L), creatinine clearance (mL/s), and total protein excretion (g/24 h) derived from 24-hour urine collections.

In all patients a detailed obstetric history was recorded at presentation that was supplemented for this study by a questionnaire sent to patients. The following were noted: the women's parity and number of live births; the gestation, sex, and birth weight of all live births; the frequency and cause of fetal loss including early (<12 wk) spontaneous abortion. Prematurity was defined as gestation lasting 36 weeks or less. Birth weights were recorded in a minority of cases but were solicited in the mailed questionnaire and enabled an assessment of the incidence of small for gestational age infants (<10th percentile of weight for gestation for the Australian population).

All women were asked if they had any complications in pregnancy including kidney problems or renal impairment, preeclampsia (explained as hypertension, proteinuria, and swelling), hypertension, or excess protein in their urine. If so, the time at which they occurred, and the treatment required including hospitalization, were recorded.

Pregnancies occurring after the diagnosis of TBMN and while under the care of the treating nephrologist were studied in more detail. These were designated *monitored pregnancies*. In addition to the fetal and maternal outcomes previously described, patients' blood pressure (patients were considered hypertensive if blood pressure exceeded 140/90 mm Hg in pregnancy), urinary red blood cell count, plasma creatinine level, 24-hour creatinine clearance, and total protein excretion were recorded prospectively before pregnancy, during the second trimester, and postpartum (3-6 months after delivery).

Statistical analysis was performed by an analysis of variance.

Results

Between 1991 and 2004, 86 women were diagnosed with TBMN on clinical features and family history alone (15 women, 17%) or on renal biopsy examination (71 women, 83%). A total of 32 patients (37%) had a known family history of hematuria.

The mean age of these women at the time of diagnosis with TBMN was 40 years (range, 19-71 y). Twelve (14%) women had a blood pressure of 150/95 mm Hg or greater[6] or were on antihypertensive medication at the time of presentation.[6]

All patients had significant glomerular hematuria with an average glomerular red blood cell count of 188 × 10^3 red blood cells/mL (counts >1 × 10^6 were recorded as 1 × 10^6 in this calculation). Three (3.5%) patients had 1 × 10^6 or greater glomerular red blood cells/ml at presentation.

Biochemical and urinary data are summarized in Table 1. All patients had a normal serum creatinine level and although 6 patients recorded a creatinine clearance of less than 1.3 mL/s, 4 of these patients were more than 40 years of age and none had a creatinine clearances less than 1 mL/s. The average 24-hour protein excretion was 0.14 g, but 19 women (22%) had an excretion rate greater than 0.15 g/24 h, including 3 women with greater than 0.5 g/24 h and 1 woman with greater than 1 g/24 h.

The 86 women undertook or had undertaken 182 pregnancies (one twin) of which 18 (17 women) were monitored. Overall fetal outcome was a live birth in 174 of the 183 fetuses (95%). Eight of the 9 fetal deaths occurred before 12 weeks' gestation (4.4%), and 1 occurred at 16 weeks in the absence of maternal complications. Four (2.2%) live births were premature. The birth weight was known or ascertained

Table 2 Thin Basement Membrane Nephropathy: Maternal Outcomes

		Trimester			Treated	
Medical Problem	Number	1st	2nd	3rd	Yes	No
No complications	147 (89.6%)	N/A			N/A	
Pre-eclampsia	3 (1.8%)			3		3
Hypertension and proteinuria	2 (1.2%)	2				2
Hypertension	10 (6%)	1		9	1	9
Proteinuria	2 (1.2%)			2		2
Total	164	3		14	1	15

NOTE. Maternal data from all nonmonitored pregnancies.

Table 3 Thin Basement Membrane Nephropathy: Maternal Outcomes

Medical Problem	Number	Trimester			Treated	
		1st	2nd	3rd	Yes	No
No complications	12 (66.7%)	N/A			N/A	
Pre-eclampsia	1 (5.6%)		1			1
Hypertension and proteinuria	1 (5.6%)	1				1
Hypertension	4 (22%)	3	1			4
Proteinuria	0		0			0
Total	18	4	2		0	6

NOTE. Maternal data only from monitored pregnancies.

by the questionnaire in 90 of 174 live births (52%) and in 4 cases (4.4%) the babies were small for gestational age. The mothers of all the small for gestational age babies had been hypertensive in pregnancy. Fetal outcome in the 18 monitored pregnancies was universally successful with 1 premature (35 weeks' gestation) infant.

Maternal outcome in the 164 nonmonitored pregnancies is shown in Table 2. None had a deterioration of renal function. Hypertension (either alone or in conjunction with proteinuria or as part of a symptom complex recalled by the patient as preeclampsia) was reported in 15 (9%) pregnancies. In only 1 case was this recalled as requiring treatment. In 2 pregnancies, proteinuria alone in the third trimester was reported.

Maternal complications for the 18 monitored pregnancies are shown in Table 3. Here hypertension was reported in 6 (33%) pregnancies, usually alone and often from the first trimester. However, hypertension was mild and in no case was drug treatment initiated.

Figure 1 shows the significantly higher mean creatinine clearance recorded during monitored pregnancies (2.6 ± 0.66 mL/s) than either before (1.7 ± 0.3 mL/s) or after pregnancy (1.8 ± 0.36 mL/s) (both $P < .001$).

Figure 2 shows individual 24-hour protein excretion values before, during, and after pregnancy. In only 1 pregnancy did proteinuria increase significantly and this change reversed postpartum. The reversible increase occurred in the monitored pregnancy with the highest prepregnancy protein excretion (0.7 g/24 h) increasing to 1.5 g/24 h in late pregnancy. Post partum (approximately 3 months), 24-hour protein excretion had decreased to 0.33 g/24 h.

Discussion

TBMN represents the single largest cause of isolated microscopic hematuria and occurs in up to 2.5% of otherwise normal adults.[8,9]

Comparison of our group of women with previously published series of adults with TBMN summarized by Savige et al[8] reveals remarkably consistent clinical features. Our patients had persistent hematuria, usually minimal, if any, pro-

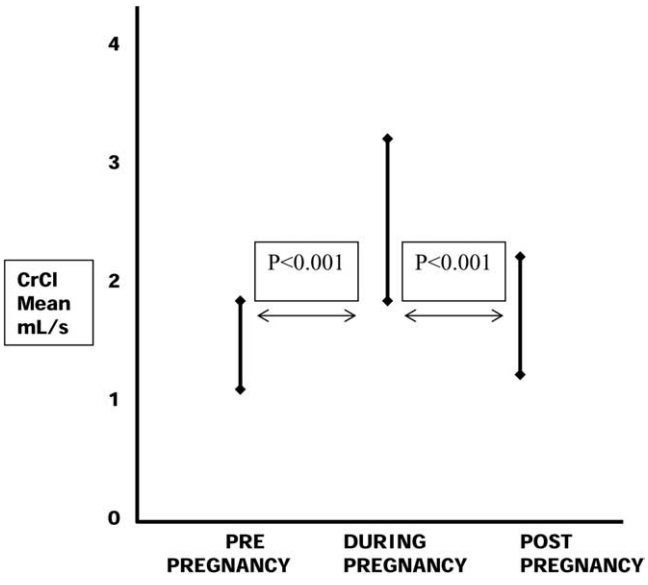

Figure 1 Serial mean creatinine clearance ± SD of 18 women with TBMN undertaking monitored pregnancies. CrCl, creatinine clearance.

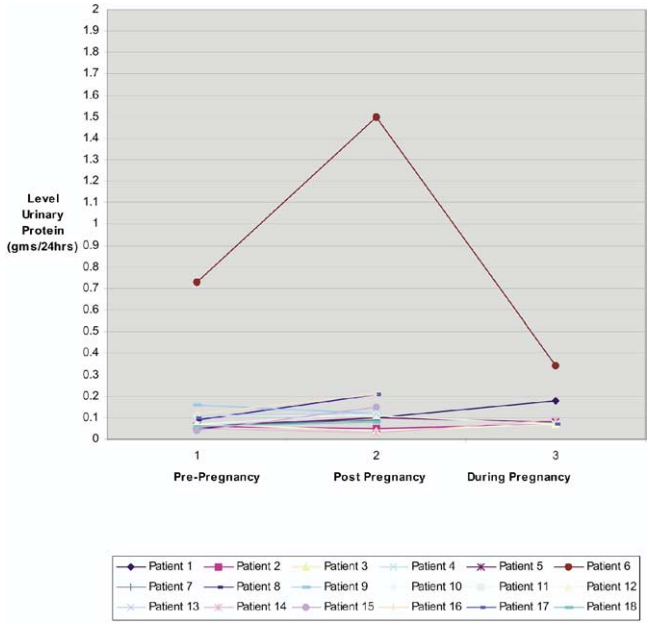

Figure 2 Serial total urinary protein levels of 18 women with TBMN undertaking monitored pregnancies.

teinuria, and normal renal function. Our incidence of hypertension was similar. We also found a positive family history of hematuria was common.

In this series, we have assumed that the genetic abnormality in TBMN is present from birth, and that adult women with the condition would have had hematuria from infancy or early adult life. Thus the retrospective analysis of obstetric history in patients in whom a confident diagnosis can be made is valid. We have limited our analysis to biopsy examination–proven cases or where a positive family history was available. Additionally, we have analyzed a smaller group of pregnancies prospectively and shown similar fetal and maternal outcomes in pregnancy.

We report excellent fetal and maternal outcome of pregnancy in women with TBMN. The incidence of early fetal loss (<12 weeks' gestation) at 4.4% is lower than the general population and probably reflects underreporting by our patients. Only 1 fetal loss occurred later in pregnancy in our series, possibly owing to placental insufficiency and unrelated to maternal renal disease. The incidence of prematurity at 2.2% approximates that of the general Australian population, as does the incidence of small for gestational age infants in our patients at 4.5%. Interestingly, maternal hypertension was recorded in each of our small for gestational age babies.

Maternal morbidity in pregnancy appears limited to hypertension. Again, the 9% incidence reported by our patients approximates that in the general population (10% to 12%),[10] but in view of the higher incidence of 33% in our albeit small series of monitored pregnancies, this again may reflect underreporting. It is striking, however, that only 1 woman remembered having to be treated for hypertension in our series. Whether women with TBMN have an increased incidence of pregnancy hypertension or not still is unclear.

The serial creatinine clearance data obtained from our monitored pregnancies shows a significant increase paralleling the 50% increase in creatinine clearance observed from the end of the first trimester and returning to prepregnancy values postpartum as described by Davison et al[11] in the normal population.

The large series addressing the question of pregnancy in primary glomerular disease were published in the 1980s,[1-6] detailing pregnancy data accumulated over preceding periods of up to 20 years. The absence of electron microscopic analysis of renal biopsy specimens probably resulted in women with TBMN receiving alternative diagnoses. Our experience and expectation is that these women were likely to have been labeled as having mild nonimmunoglobulin A mesangial proliferative glomerulonephritis and we previously published our experience of pregnancy in patients with this diagnosis.[12] We reported 168 pregnancies in 91 women with an overall fetal loss of 20% and a late fetal loss rate of 12%. Three percent of women developed renal impairment during pregnancy, 48% developed hypertension, and 53% developed proteinuria. However, in every case, renal impairment was reversible postpartum and hypertension and proteinuria persisted postpartum in only 7% and 1% of women, respectively. However, in comparison with our current series, this incidence of fetal and maternal complication seems much increased. Nevertheless, this histologic group represented the best outcome of pregnancy in our overall experience of primary renal disease.[6] The confounding factor, however, was that only a minority of patients in our 1988 series had been diagnosed before their first analyzed pregnancy and, indeed, the great majority had been diagnosed because of a previous complicated pregnancy that was included in the analysis. Extrapolation of this experience to a group of patients diagnosed before pregnancy is not valid.

In summary, this series based on the obstetric history of an unselected group of parous women with TBMN presenting to a general adult nephrology practice over a 13-year period, indicates that their pregnancy is without significantly increased risk compared with the normal population in terms of maternal and fetal outcome.

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