Microalbuminuria after pregnancy complicated by pre-eclampsia

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Abstract

**Background.** Microalbuminuria is an important risk factor for underlying vascular disease. Its detection after pregnancy complicated by pre-eclampsia may have predictive value for the later development of chronic hypertension or renal disease.

**Method.** The study group consisted of 48 women in whom pregnancy had been complicated by pre-eclampsia. Urinary albumin excretion rate, blood pressure, and renal function parameters were assessed 2–4 months and 3–5 years after the pregnancy. Results were compared with those in 44 women after normal pregnancy.

**Results.** Mean urinary albumin excretion rate was significantly higher in the study group than in the controls both at 2–4 months after delivery (27.0 ± 33 vs 6.1 ± 3.3 mg/24 h) and at 3–5 years after delivery (23.5 ± 26.8 vs 6.7 ± 2.8 mg/24 h) (\(P = 0.001\)). The rate of occurrence of microalbuminuria was not significantly different between the early (58%) and late (42%) time-points within the study group or between the nulliparous and the multiparous women.

**Conclusions.** A history of pregnancy complicated by pre-eclampsia is associated with a high occurrence of microalbuminuria. Whether the presence of microalbuminuria reflects a possible underlying vascular disease in affected patients needs to be further investigated in large-scale studies.

Key words: microalbuminuria; pre-eclampsia; post-delivery

Introduction

Microalbuminuria (MA) continues to be a matter of concern in patients with hypertension even in the absence of diabetes mellitus [1]. Recent studies have pointed to the importance of MA as a risk factor for end-organ damage, such as left ventricular hypertrophy, myocardial infarction, stroke, peripheral vascular disease, and retinopathy, independent of blood pressure (BP) [2–4].

In pregnancy, the occurrence of MA dictates close follow-up for pre-eclampsia [5]. It is claimed that women with hypertensive disorders during pregnancy are at an increased risk of chronic hypertension later in life [6]. Since renal involvement is a prerequisite for the diagnosis of pre-eclampsia, it is possible that hypertension at follow-up in previously pre-eclamptic women is associated with residual renal disorders [7,8]. Therefore, the presence of MA after pregnancy complicated by pre-eclampsia may also be of value in predicting future development of chronic hypertension, residual renal abnormality, or other underlying vascular disease.

The aim of the present study was to assess the occurrence of MA in women in whom an earlier pregnancy had been complicated by pre-eclampsia.

Subjects and methods

The study and control group allocation was based on the follow-up of 276 women who participated in a previous study on MA in pregnancy [5]. The study population consisted of women who were referred from community clinics to the Hypertension in Pregnancy Clinic at Rabin Medical Centre during 1990–1993 because of high blood pressure (BP) during pregnancy, and were found to have pre-eclampsia. Pre-eclampsia was defined as BP ≥ 140/90 mmHg and urinary protein excretion ≥ 300 mg/24 h after 20 weeks of gestation. None of the women had a definite diagnosis of chronic hypertension or renal disease and all were untreated before the clinic visit. BP was measured by a specially trained nurse using a standard sphygmomanometer. Arm circumference was measured, and a cuff with a larger bladder was used for arms larger than 32 cm. The recorded value was the mean of three measurements made on the right arm with the subject supine for 10 min. The fifth Korotkoff sound was used as the diastolic BP. For the definition of pre-eclampsia at least two BP measurements, 6 h apart, were taken into consideration. Proteinuria was determined after a 24-h urine collection. The control group was composed of healthy women, mostly from hospital staff, who had had a pregnancy uncomplicated by hypertension during the same period. Only
women who had not had another pregnancy between the index pregnancy and the second time point of the present study (see below) were selected for the study. Two of the 50 women in the study group and six of the 50 women selected as controls were lost to follow-up (96 and 88% compliance rate respectively).

All participants were given a full explanation of the study and signed an informed consent form.

Examination of the study and control groups was performed at two time-points: 2–4 months after delivery and 3–5 years after delivery. The examination included measurement of systolic and diastolic BP and simultaneous analysis of plasma concentrations of blood urea nitrogen, creatinine, uric acid and urinary creatinine clearance with the hydroxylamine method (SMA 12/60, Technicon, Tarrytown, PA, USA).

Samples from an 8-h overnight urine collection were sent for immediate radioimmunoassay for MA; $^{125}$Ialbumin and antialbumin antibodies were used, as described by Christensen and Orskov [9], with a modification developed in our laboratory [10]. The intra-assay and interassay coefficients of variation are 6 and 5.6% respectively, with a sensitivity of 1.5 mg/l or 2 mg/24 h for urine samples with albumin concentrations of 20 mg/l and 100 mg/l. In addition, urinalysis and urine culture were also performed for each patient before beginning the urine collections to exclude the possibility of a urinary tract infection (UTI). Women with positive findings for UTI were re-examined after proper treatment.

MA was defined as urinary albumin excretion rate (AER) higher than 14 mg/24 h, in accordance with the results of Erman et al. [11] of a normal non-pregnant population (mean ± 2SD).

Statistical analysis

Values are expressed as mean and SD. Urinary AERs were not distributed normally in the study and control groups and were therefore logarithmically transformed before calculation. The AER results between groups were compared by t-test for equality of means with equal variances not assumed, and between the two time-points by McNemar test. A P value ≤0.05 was considered statistically significant.

Results

The basal and pregnancy outcome characteristics of the study and control groups are summarized in Table 1. Mean age of the subjects at 3–5 years after delivery was 35 ± 5 years for the study group and 35 ± 8 years for the control group; nulliparity rates were 23 and 25% respectively. Neither of these differences was significant. A worse pregnancy outcome in terms of preterm delivery, intrauterine growth restriction and hospitalization in a neonatal unit was observed in the patients with pre-eclampsia as compared to controls (Table 1). Table 2 summarizes the urinary AER values in the study and control groups and Table 3 shows the results of the BP and renal function measurements. Both early and late mean AERs were significantly higher in the study group than the control group ($P=0.001$), as were the mean systolic and diastolic BP ($P=0.00001$). There were no significant intergroup differences for any of the other renal function parameters (Table 3) were observed between the nulliparous and multiparous women in the study group throughout the study period. No significant differences in AER and occurrence of MA (Table 2) or in BP and other renal function parameters (Table 3) were observed between the nulliparous and multiparous women in the study group. Of the 48 women, 20 (42%) in the early period and 14 (29%) in the late period were found to have BP values above 140/90 mmHg or were receiving antihypertensive medications ($P=0.286$). None of the other parameters studied showed a significant difference between the early and late post-delivery periods in the study group (Table 3). In the 14 patients with evidence of chronic hypertension (BP values above 140/90 mmHg or on antihypertensive treatment), MA was detected in only 4 (28%) at 3–5 years after a complicated pregnancy.

Discussion

The present study demonstrates that women who 3–5 years earlier had a pregnancy complicated by pre-eclampsia have a higher rate of occurrence of MA than women with uncomplicated pregnancies, though there are no differences between these groups in renal function. Research has shown that proteinuria and albuminuria are important indicators of renal disease in both diabetic and non-diabetic patients [12]. Regarding diabetic patients, it is well established that diabetic nephropathy is preceded by several years by the appearance of MA. We suggested in a previous report, similar to the present one, that the 30% occurrence rate of MA noted at 5–8 years after pregnancy complicated by gestational diabetes mellitus may well
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Table 2. Urinary AER (mg/24 h) (mean ± SD) and occurrence of MA 2–4 months and 3–5 years after delivery in the study and control groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>2–4 months after delivery</th>
<th>3–5 years after delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AER</td>
<td>MA</td>
</tr>
<tr>
<td>Nulliparous women ( (n=11) )</td>
<td>19 ± 15</td>
<td>6 (54%)</td>
</tr>
<tr>
<td>Multiparous women ( (n=37) )</td>
<td>29 ± 44</td>
<td>22 (62%)</td>
</tr>
<tr>
<td>Total ( (n=48) )</td>
<td>27 ± 33*</td>
<td>28 (58%)</td>
</tr>
<tr>
<td>Control group ( (n=44) )</td>
<td>6.1 ± 3.3</td>
<td>0 (0%)</td>
</tr>
</tbody>
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\[ P = 0.001 \text{ for difference from controls for ln (AER) at the two time-points. AER, albumin excretion rate; MA, microalbuminuria.} \]

Table 3. Blood pressure and renal function (mean ± SD) in study and control subjects 2–4 months (A) and 3–5 years (B) after delivery

<table>
<thead>
<tr>
<th>Study group</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>Serum creatinine (mg/dl)</th>
<th>Serum uric acid (mg/dl)</th>
<th>Urinary creatinine clearance (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Nulliparous women ( (n=11) )</td>
<td>129 ± 12*</td>
<td>130 ± 12*</td>
<td>87 ± 9*</td>
<td>86 ± 8*</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Multiparous women ( (n=37) )</td>
<td>134 ± 14*</td>
<td>134 ± 17*</td>
<td>88 ± 10*</td>
<td>89 ± 10*</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Total ( (n=48) )</td>
<td>132.2 ± 13.1*</td>
<td>132.8 ± 16.2*</td>
<td>87.2 ± 9.6*</td>
<td>87.9 ± 8.7*</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>Control group ( (n=44) )</td>
<td>115 ± 11.2</td>
<td>118 ± 12</td>
<td>73.4 ± 6.5</td>
<td>77.2 ± 8.0</td>
<td>0.9 ± 0.3</td>
</tr>
</tbody>
</table>

\[ P = 0.00001 \text{ for different from controls for systolic and diastolic BP at the two time-points.} \]

indicate that MA is a sign of early renal disease [13]. Indeed, also in non-diabetic patients, MA was found to be correlated with higher BP [1] and end-organ damage [2]. Thus, despite the lesser known prognostic role of MA in the evolution of hypertension and renal disease, the high (42%) incidence of MA noted here in women with a history of pre-eclampsia may be of clinical importance. Moreover, it was interesting that we detected MA in only 28% of the women with evidence of chronic hypertension at 3–5 years after a complicated pregnancy.

To the best of our knowledge, there is only one follow-up study of patients with hypertensive disorders in pregnancy in which MA was assessed [14]. These authors reported a 20 and 14% rate of MA in women with a history of pre-eclampsia and pregnancy-induced hypertension (PIH) respectively. However, they used a semiquantitative method to detect MA, which is known to be less sensitive than the radioimmunoassay technique applied here. Although it is accepted that PIH carries an increased risk of future hypertension [6], the role of pre-eclampsia in hypertension has long been a matter of debate. Most authors today assume that pre-eclampsia is in some way associated with an increased risk of hypertension compared with normotensive pregnancy [15], and that it is differences in patient populations and methods of selection in the various studies that probably account for the wide reported range (8–67%) in underlying renal disease and chronic hypertension [8,16]. There are, however, a few points that need clarification before we reach a definitive conclusion regarding the association of MA after pregnancy complicated by pre-eclampsia with a higher risk of underlying glomerular disease. Firstly, the similar occurrence of MA at 2–4 months (58%) and at 3–5 years (42%) after delivery in the study group, combined with the absence of MA in the control group, suggests that in patients with pre-eclampsia, there is a slower resolution of gestationally mediated renal changes (expressed by higher AER) than in women after uncomplicated pregnancy. These results are in agreement with other investigators [16,17], suggesting that MA may result from pre-eclampsia rather than reflect an underlying disease that causes it.

Secondly, our selection of mostly multiparous women (77%) and nulliparous women with high BP in the early stages of pregnancy may have yielded a population with a high incidence of underlying but undiagnosed disease. Thirdly, by using the McNemar test, we observed no correlation between the early and the late examination of MA after delivery in the study group patients. Lastly, pregnancy-mediated alterations in circadian albumin excretion [18] may have biased the comparison by 8-h overnight AER between the two time-points after delivery.

In conclusion, our findings of a high incidence of MA after pregnancy complicated by pre-eclampsia call for controlled, long-term follow-up studies to determine conclusively whether patients who have had pre-eclampsia should be screened for the presence of MA.
after delivery in order to identify those at risk of glomerular disease.

References


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