Is proteinuric pre-eclampsia a different disease in primigravida and multigravida?

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ABSTRACT

This study aimed to identify if the clinical features of proteinuric pre-eclampsia or the biochemical markers of endothelial dysfunction associated with this syndrome are altered according to parity in a direction that would suggest a different pathophysiology. Groups of 27 primigravid and 35 multigravid women with pre-eclampsia (defined as blood pressure > 140/90 mmHg and 2+ proteinuria) were studied ante-partum, and at 6 weeks and 6 months post-partum. Clinical markers of severity of pre-eclampsia, including blood pressure, markers of renal, hepatic and coagulatory function, and biochemical markers of endothelial dysfunction were measured. Fetal outcome was assessed by birthweight and birthweight percentile. Ante-partum systolic blood pressure was 10 mmHg higher in the primigravida, and this difference was independent of age and anti-hypertensive medication. Analysis of systolic blood pressure before and after delivery showed the primigravid women to have elevated systolic blood pressure over the whole time period (P < 0.01). The primigravid women had more severe hepatic dysfunction, with elevated aspartate aminotransferase levels, but plasma creatinine, proteinuria, platelet counts and haematocrit were similar, indicating that renal and coagulatory function and plasma volume were affected to the same extent in the two groups and were independent of parity. Birthweight was similar in the two groups, and the percentage of infants weighing less than the 10th centile for gestation was also similar. Biochemical markers of endothelial dysfunction, assessed by measuring the urinary prostacyclin metabolite 2,3-dinor-6-oxo-prostaglandin F1α and plasma endothelin 1, did not differ according to parity. There were no differences in a number of other biochemical markers of pre-eclampsia, including plasma albumin, uric acid, triacylglycerol, and total, low-density lipoprotein and high-density lipoprotein cholesterol. Basophil, monocyte and lymphocyte counts were elevated before delivery in primigravid women with pre-eclampsia. The differences in lymphocyte counts persisted post-partum. Further studies are required to clarify the role, if any, of monocytes, basophils and lymphocytes in the pathophysiology of pre-eclampsia. In conclusion, the elevated systolic blood pressure and raised aspartate aminotransferase levels observed in primigravida suggest a more severe form of pre-eclampsia. The lack of differences in birthweight and other biochemical and endothelial markers of severity of pre-eclampsia do not suggest a different pathophysiology; however, the persistently higher white cell counts in the primigravida pre-eclamptics are of interest, and might reflect differences in immune responses in the two groups. We suggest that studies of the pathophysiology of pre-eclampsia should include multigravida, as long as there is adequate post-partum follow-up to exclude underlying disease.

Key words: hypertension, lymphocytes, monocytes, parity, pre-eclampsia, proteinuria.

Abbreviations: ANOVA, analysis of variance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PGF1, prostaglandin F1α; SBP, systolic blood pressure.

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INTRODUCTION

This study examines whether there are identifiable differences in pathophysiological features of proteinuric pre-eclampsia according to whether the condition occurs in first or subsequent pregnancies. Although defined by elevated blood pressure and proteinuria, pre-eclampsia is a multisystem disorder with impairments of renal, hepatic and coagulatory function, and is also characterized by endothelial dysfunction [1]. Evidence suggesting that the pathophysiology of primigravid pre-eclampsia may differ from that observed in multigravida comes from studies showing that the prevalence of pre-eclampsia in a first pregnancy is 15 times greater than that for a full-term second pregnancy [2]. In addition, glomerulonephritis, which has been suggested to reflect an accurate clinical diagnosis of pre-eclampsia and which provides morphological evidence of renal endothelial damage, was found to be much less common in multigravida who had pre-eclampsia [3]. Chesley [4] noted that multiparous women who had eclampsia had an increased incidence of underlying disease, while Gleishner et al. [5] observed that multipara with pre-eclampsia showed an earlier increase in blood pressure and a greater weight gain than primipara. In the same study, the offspring of pre-eclamptic multipara were smaller relative to those of multiparous controls than infants born to primipara. These findings suggested to both sets of authors that the pathophysiology of pre-eclampsia may differ according to parity.

A number of factors could contribute to pre-eclampsia in multigravida; these include altered paternity, consistent with the immunological theory of an inappropriate response to new paternal fetal antigens [6], and acquired factors sensitizing patients to the disorder. It is likely that no single cause will explain all cases of pre-eclampsia, and that a number of different underlying factors could operate to result in the development of pre-eclampsia.

The present study aimed, first, to identify whether there are clinical features of proteinuric pre-eclampsia that distinguish primigravid from multigravid women, suggesting a different pathophysiology. The parameters examined included blood pressure and factors related to renal, hepatic and haematological abnormalities commonly observed in the syndrome. As morphological evidence of glomerulonephritis has been reported to differ between primigravid and multigravid pre-eclampsics, a secondary aim was to examine biochemical markers of endothelial dysfunction. The markers measured included urinary 2,3-dinor-6-oxo-prostaglandin F\textsubscript{1α}, a marker of systemic prostacyclin synthesis, and plasma endothelin 1, both of which have been shown to be altered in pre-eclampsia in a direction that suggests endothelial dysfunction [7–10]. Although plasma lipid levels and leucocyte counts are not usually measured as part of the clinical management of pre-eclampsia, they were examined in the present study because they have been shown to be consistently elevated in pre-eclampsia [7,11–13], and because of the potential for activated leucocytes or an altered lipid profile to contribute to endothelial dysfunction [14,15]. Clinical markers of pre-eclampsia were examined, taking into account familial and lifestyle factors that may have affected the measurements. Patients were studied at hospital admission and twice after delivery to determine whether any differences distinguishing the two groups persisted in the non-pregnant state.

METHODS

Subjects
 Altogether, 27 primigravid and 35 multigravid women were recruited at the King Edward Memorial Hospital between 1991 and 1995 for studies investigating the pathophysiology of pre-eclampsia [7,11,12,16,17]. They gave their informed consent to participate in the study, which was approved by the King Edward Memorial Hospital for Women and the University of Western Australia ethics committees. Pre-eclampsia was defined as the development of blood pressure greater than 140/90 mmHg after 20 weeks’ gestation, combined with proteinuria of at least 2+, in women with no known history of hypertension or renal disease and whose blood pressure had returned to normal levels by 6 months post-partum with no continuing proteinuria. All the women were studied on referral to the research nurse prior to delivery, and at 6 weeks and 6 months post-partum.

Assessment of obstetric and medical history, family history of disease and lifestyle factors
 At an antenatal visit, all the women answered a questionnaire relating to their obstetric and medical history, including changes in paternity for multigravida, medication usage and lifestyle habits, including alcohol consumption and smoking. An assessment of family history of disease was made by administration of a questionnaire that asked the women if they had any family history of high blood pressure, stroke, diabetes or renal disease. If they answered in the affirmative, they were asked specifically which family member had been affected. Inquiry was also made into the obstetric history of each subject’s mother and whether she had suffered from pre-eclampsia, pregnancy-induced hypertension or toxaemia during any of her pregnancies. The women reported their current smoking habits and alcohol consumption in the previous week. Statistical analysis was confined to Caucasian women who had no previous history of...
diabetes, hypertension or renal disease. Parity of the subjects was determined from their medical records and the questionnaire administered by a research nurse. Women who reported having terminations or spontaneous abortions were classified as multigravida, and their gravid status was confirmed by hospital records. The multigravid women were asked if they had previously had pre-eclampsia, and whether they had a different partner from the previous pregnancy.

**Maternal clinical measurements**

**Blood pressure and heart rate**
The women were enrolled in the study after hospital admission. Sixteen primigravida and 20 multigravida were attending the antenatal clinics prior to admission and had blood pressure recorded between 22 and 28 weeks’ gestation as part of their clinical management. The remaining nine primigravida and 15 multigravida were referred from remote sites with a referral letter stating that their blood pressure during pregnancy had been normal until the time of diagnosis and transfer. The blood pressure at admittance used for entry into the study was the initial measurement recorded by the resident doctor on the antenatal ward using a manual sphygmomanometer. Upon entry into the study and at 6 weeks and 6 months post-partum, blood pressure was measured by the same research nurse using a Dinamap 1846 SX oscillometric monitor. The women were studied prior to delivery in the antenatal ward. Post-partum study of the women took place at either the hospital outpatient clinic or the subject’s home. Systolic and diastolic blood pressure and heart rate for each visit was the average of six Dinamap readings taken at 1 min intervals after 5 min of seated rest.

**Biochemical and haematological measurements**
At each visit, 24 h urine was collected and a non-fasting blood sample was obtained from the antecubital vein by the research nurse, after 10 min of seated rest. Plasma uric acid, albumin and urinary protein excretion were measured as markers of severity of pre-eclampsia, using a COVAS-MIRA analyser in the Biochemistry Department, Royal Perth Hospital. Plasma creatinine was measured as a marker of renal impairment using the same research nurse using a Dinamap 1846 SX oscillometric monitor. The women were studied prior to delivery in the antenatal ward. Post-partum study of the women took place at either the hospital outpatient clinic or the subject’s home. Systolic blood pressure at admittance used for entry into the study was the initial measurement recorded by the resident doctor on the antenatal ward using a manual sphygmomanometer. Upon entry into the study and at 6 weeks and 6 months post-partum, blood pressure was measured by the same research nurse using a Dinamap 1846 SX oscillometric monitor. The women were studied prior to delivery in the antenatal ward. Post-partum study of the women took place at either the hospital outpatient clinic or the subject’s home. Systolic and diastolic blood pressure and heart rate for each visit was the average of six Dinamap readings taken at 1 min intervals after 5 min of seated rest.

**Biochemical markers of endothelial dysfunction**
Systemic prostacyclin synthesis, which has been found previously to be reduced in women with pre-eclampsia, was assessed by measuring the urinary prostacyclin metabolite 2,3-dinor-6-oxo-PGF$_2$α by radioimmunoassay after extraction and purification by TLC [7]. Plasma endothelin 1, which has been shown previously to be raised in women with pre-eclampsia, was measured by radioimmunoassay after extraction, as described previously [7].

**Fetal outcome measures**
Details of infant birthweight and postnatal complications were obtained from hospital records. The baby’s birthweight percentile was determined using Australian standardized birthweight scales that take into account parity, the sex of the infant and the mother’s height.

**Statistical analysis**
Results are expressed as means ± S.E.M. Differences in familial and lifestyle factors were assessed using Chi-square analysis. Differences between primigravida and multigravida were assessed using an unpaired t-test or, where data were not normally distributed, the Mann–Whitney test. A Bonferroni correction was used to correct for multiple testing. Antepartum blood pressure differences between the pre-eclamptic primigravida and multigravida were assessed by ANOVA (analysis of variance) after adjustment for differences in age and duration of anti-hypertensive treatment. Differences in systolic blood pressure (SBP) over time were assessed by unpaired t-test after calculation of the area under the curve for primigravida and multigravida.

**RESULTS**
The primigravid and multigravid women were studied at similar gestations: 31.4 ± 0.6 weeks in the primigravid women and 30.8 ± 0.6 weeks in multigravida. The primigravid women were, as expected, younger (Table 1).

**Differences in family history and lifestyle factors in relation to parity**
The primigravid and multigravid women were similar with respect to family history of hypertension (64% primigravid, 65.7% multigravida), stroke (24% primigravid, 22.9% multigravida), diabetes (28% primigravid, 28.6% multigravida) and renal disease (0% primigravid, 5%
Table 1  Age, body mass index (BMI) and blood pressure before and after delivery, and anti-hypertensive treatment

<table>
<thead>
<tr>
<th></th>
<th>Primigravida</th>
<th>Multigravida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>25.9 ± 0.9</td>
<td>28.7 ± 1.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>29.2 ± 0.7</td>
<td>29.7 ± 1.1</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>25.6 ± 0.9</td>
<td>27.0 ± 1.2</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>26.6 ± 1.0</td>
<td>26.1 ± 1.3</td>
</tr>
<tr>
<td>Admitting blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>159 ± 3</td>
<td>152 ± 4</td>
</tr>
<tr>
<td>DBP</td>
<td>98 ± 4</td>
<td>99 ± 2</td>
</tr>
<tr>
<td>Dinamap SBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>138 ± 2*</td>
<td>128 ± 2</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>116 ± 2</td>
<td>113 ± 2</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>117 ± 2</td>
<td>112 ± 2</td>
</tr>
<tr>
<td>Dinamap DBP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>78 ± 2</td>
<td>75 ± 2</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>70 ± 2</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>70 ± 2</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>76 ± 3</td>
<td>83 ± 3</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>78 ± 2</td>
<td>79 ± 2</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>77 ± 2</td>
<td>78 ± 2</td>
</tr>
<tr>
<td>Anti-hypertensive treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>56% (15)</td>
<td>60% (21)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>7% (2)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

multigravida). The reported family history of maternal pre-eclampsia was similar in the two groups (52.4% primigravida, 38.5% multigravida). Only one subject reported having changed partner since her last pregnancy. Of the multigravida women, 43% reported that they had previously suffered from pregnancy-induced hypertension. The percentage of women currently smoking before delivery was similar in the primigravida and multigravida (18.5% and 12.1% respectively), as was the percentage that had consumed alcohol in the previous week (11.1% of primigravida compared with 15.2% of multigravida).

Differences in anthropometry, heart rate and blood pressure in relation to parity

There were no between-group differences in body mass index or heart rate before delivery, or at 6 weeks or 6 months post-partum (Table 1). Antenatal clinic blood pressures were obtained from medical records for the period between 22 and 28 weeks’ gestation, before the onset of clinical symptoms, and these averaged 120/72 ± 1.9/1.4 mmHg in the 16 primigravida and 120/73 ± 2.6/1.3 mmHg in the 20 multigravida assessed.

Blood pressure recorded by manual sphygmomanometer on admission to hospital showed a non-significant trend to higher levels in the primigravida. Antenatal SBP measured using a Dinamap recorder was significantly elevated in the primigravida women compared with the multigravida women (P < 0.004) (Figure 1, Table 1). Although SBP fell in both groups after delivery (examined as area under the curve before and after delivery), the primigravida women had significantly higher SBPs compared with the multigravida women over the whole time period (P = 0.015) (Figure 2). Diastolic blood pressure measured by Dinamap tended to be higher in the primigravida women both before and after delivery, but the difference did not achieve statistical significance (Table 1).

The number of the women receiving anti-hypertensive medication at the time they were studied was similar in the two groups (Table 1). The treatment consisted mainly of α-methyldopa and nifedipine. For these reasons, the analysis was repeated using ANOVA with adjustment for differences in age and duration of medication. The
Table 2  Biochemical markers of pre-eclampsia in primigravid and multigravid women

<table>
<thead>
<tr>
<th></th>
<th>Primigravida</th>
<th>Multigravida</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antenatal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma aspartate aminotransferase (units/l)</td>
<td>$53.1 \pm 9.6$ ($n = 26$)</td>
<td>$26.2 \pm 6.9$ ($n = 31$)</td>
</tr>
<tr>
<td>Plasma alkaline phosphatase (units/l)</td>
<td>$145 \pm 37.7$ ($n = 26$)</td>
<td>$139 \pm 6.9$ ($n = 31$)</td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>$7.2 \pm 0.5$ ($n = 26$)</td>
<td>$7.6 \pm 0.7$ ($n = 31$)</td>
</tr>
<tr>
<td><strong>Plasma albumin (g/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>$31.2 \pm 0.6$</td>
<td>$31.0 \pm 0.5$</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>$43.1 \pm 0.5$</td>
<td>$42.4 \pm 0.5$</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>$43.4 \pm 0.6$</td>
<td>$42.3 \pm 0.5$</td>
</tr>
<tr>
<td><strong>Plasma uric acid (mmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>$0.38 \pm 0.02$</td>
<td>$0.35 \pm 0.02$</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>$0.31 \pm 0.01$</td>
<td>$0.30 \pm 0.01$</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>$0.27 \pm 0.01$</td>
<td>$0.26 \pm 0.01$</td>
</tr>
<tr>
<td><strong>Plasma creatinine (µmol/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>$70.1 \pm 2.5$</td>
<td>$70.4 \pm 2.1$</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>$71.3 \pm 1.8$</td>
<td>$75.3 \pm 2.0$</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>$74.5 \pm 1.8$</td>
<td>$76.7 \pm 2.4$</td>
</tr>
<tr>
<td><strong>Urinary protein (g/24 h)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>$2.20 \pm 0.4$</td>
<td>$1.60 \pm 0.4$</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>$2.00 \pm 0.03$</td>
<td>$0.27 \pm 0.05$</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>$2.24 \pm 0.05$</td>
<td>$0.29 \pm 0.04$</td>
</tr>
</tbody>
</table>

$P = 0.015$ for primigravid compared with multigravid women.

10 mmHg difference in antenatal SBP was found to persist after this adjustment ($P = 0.004$). The treated and untreated primigravid and multigravid women were similar with respect to gestation at sampling, and the differences in age were similar to those of the group as a whole. When SBP was examined in terms of whether the women were receiving anti-hypertensive treatment, the primigravid women had a significantly higher SBP regardless of treatment. SBP was $134 \pm 3.0$ mmHg in untreated primigravid compared with $125 \pm 3.1$ mmHg in untreated multigravid women ($P < 0.05$), while in the treated primigravid SBP was $140 \pm 3.0$ mmHg compared with $130 \pm 2.8$ mmHg in treated multigravid ($P < 0.05$). The duration of anti-hypertensive treatment before entry into the study was 24 h or less in 86% of primigravid women and 75% of multigravid women.

Effect of parity on biochemical and haematological markers of pre-eclampsia

There were no significant differences in plasma albumin, uric acid or creatinine, or urinary protein, between the primigravid and multigravid women either before delivery or at any post-partum visit (Table 2). Proteinuria was first detected at a similar stage of gestation in both groups. Prior to delivery, the primigravid women had significantly higher levels of aspartate aminotransferase activity compared with multigravid, with 11 of the 23 primigravid women having levels outside the normal limits for the measurement, compared with three of 26 measured in the multigravid group (Table 2). Antenatal levels of alkaline phosphatase were raised compared with the normal range; however, the levels were not affected by parity. The levels of bilirubin were similar in primigravid and multigravid (Table 2). Although not used in the clinical management of pre-eclampsia, plasma triacyl-
Table 3  Markers of endothelial dysfunction and lipids in primigravid and multigravid pre-eclamptic women

<table>
<thead>
<tr>
<th></th>
<th>Primigravia</th>
<th>Multigravia</th>
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<tbody>
<tr>
<td>Urinary 2,3-dinor-6-oxo-PGF$_{1\alpha}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>1697 ± 281</td>
<td>1696 ± 379</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>1110 ± 191</td>
<td>1540 ± 424</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>1208 ± 328</td>
<td>1021 ± 221</td>
</tr>
<tr>
<td>Plasma endothelin 1 (pg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>8.4 ± 1.5</td>
<td>7.0 ± 1.0</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>5.9 ± 0.6</td>
<td>4.8 ± 0.3</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>6.1 ± 0.7</td>
<td>5.3 ± 0.5</td>
</tr>
<tr>
<td>Serum triacylglycerol (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>3.51 ± 0.34</td>
<td>3.29 ± 0.29</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>1.28 ± 0.17</td>
<td>1.30 ± 0.16</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>1.26 ± 0.16</td>
<td>1.61 ± 0.38</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>6.99 ± 0.41</td>
<td>7.22 ± 0.42</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>5.78 ± 0.35</td>
<td>5.81 ± 0.31</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>5.56 ± 0.40</td>
<td>5.40 ± 0.23</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>3.55 ± 0.29</td>
<td>3.96 ± 0.36</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>3.73 ± 0.34</td>
<td>3.97 ± 0.29</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>3.56 ± 0.45</td>
<td>3.43 ± 0.16</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ante-partum</td>
<td>1.80 ± 0.12</td>
<td>1.67 ± 0.09</td>
</tr>
<tr>
<td>6 weeks post-partum</td>
<td>1.47 ± 0.08</td>
<td>1.33 ± 0.06</td>
</tr>
<tr>
<td>6 months post-partum</td>
<td>1.42 ± 0.09</td>
<td>1.22 ± 0.05</td>
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</table>

Glycerols and cholesterol were measured because they have been shown consistently to be raised in pre-eclampsia. However, in the present study there was no effect of parity on triacylglycerols or on total, LDL or HDL cholesterol, either before or after delivery (Table 3).

There were no differences in haemoglobin concentration or haematocrit between the groups (Table 4). There was no evidence that platelet consumption was different between the groups, with platelet counts having similar values (Table 4). Three primigravida and three multigravida had a platelet count of less than 150 $\times$ 10$^9$/litre.

Leucocyte counts were measured before and after delivery, because they have been shown previously to be elevated in pre-eclampsia, and because of the potential for activated leucocytes to contribute to endothelial damage. Leucocyte counts were not different between the groups at any time (Table 4). Neutrophil counts tended to be higher in primigravida before delivery, but not significantly so (Table 4). There were, however, elevations of lymphocyte, monocyte and basophil counts in the primigravida women relative to the multigravida before delivery (Table 4). At the post-partum visits, lymphocyte counts were still higher in the primigravida women, and examination of lymphocyte counts before and after delivery using area under the curve showed the levels to be significantly higher in the primigravida women over this time period ($P < 0.01$) (Figure 3).

**Effect of parity on biochemical markers of endothelial dysfunction**

The levels of the urinary metabolite of prostacyclin, 2,3-dinor-6-oxo-PGF$_{1\alpha}$, were similar in the two groups before and after delivery. Similarly, levels of plasma endothelin 1 were not affected by parity either before or after delivery (Table 3).

**Effect of parity on fetal outcome**

Over 70% of the women in both groups were delivered by caesarean section. Gestation at delivery was similar...
in primigravida (32.3 ± 0.7 weeks) and multigravida
(32.0 ± 0.6 weeks). The birthweights of infants born to
primigravid women with pre-eclampsia averaged
1728 ± 143 g, and this was similar to that of those born to
multigravid mothers (1708 ± 167 g). For the primigravid
women, 65% of babies had birthweights lower than the
10th centile for gestation (indicative of growth retardation),
compared with 64% in the multigravid group.

DISCUSSION

This study examined clinical markers of pre-eclampsia
and biochemical markers of endothelial dysfunction in
women with proteinuric pre-eclampsia, seeking
differences according to parity that might suggest a
difference in pathophysiology.

Although blood pressure recorded by resident staff on
admission to hospital did not differ between primigravid
and multigravid women with pre-eclampsia, the entry
Dinamap SBP was 10 mmHg higher in primigravid
women than in their multigravid counterparts. This
difference was not explained by differences in gestation,
which was similar in the two groups at the time of blood
pressure measurement, and occurred in spite of the
younger age of the primigravida. Indeed, the differences
were independent of age, the presence or absence of anti-
hypertensive therapy, the duration of anti-hypertensive
medication, and smoking and alcohol consumption. In
primigravid women, there was a non-significant tendency
for SBP to be elevated in subjects with a family history of
hypertension, but no such trend was seen in multigravid
women. Familial hypertension may possibly predispose
women to develop pre-eclampsia in first pregnancies.

Our findings contrast with those of Gleishner et al. [5],
who found that blood pressure elevation occurred earlier
in pregnancy in multigravid pre-eclampsia, and that
weight gain between this time and delivery was greater in
multigravid than in primigravid women. Although the
full time course of blood pressure change was not
available for all the women we studied, in those who had
attended outpatient clinics the average blood pressure
between 22 and 28 weeks’ gestation (prior to the onset of
clinical symptoms) was not different between groups.
Gleishner et al. [5] also noted that the higher blood
pressure in multigravid women was associated with
reduced fetal birthweight in this group compared with
multigravid control subjects, and reasoned that this may
represent a difference in pathophysiology. Our study
contrasts with the results of Gleishner et al. [5], in that
birthweight did not differ according to parity and similar
numbers of babies showed severe growth retardation
independent of parity. The different findings may be
explained in part by differences in subject selection. We
studied severe cases of proteinuric pre-eclampsia that
presented at around 30 weeks, whereas the report of
Gleishner et al. [5] made no mention of proteinuria; their
patients had a later onset of hypertension, and the babies
were delivered later and were less growth-retarded.

At 6 months after delivery, SBP, although within the
normal range, tended to be higher in primigravida
compared with the multigravid women. This finding
does not support previous studies suggesting that multi-
gravid women who get pre-eclampsia have underlying undiagnosed hypertension [4]. Increased systemic
vascular resistance [16] and reduced aortic size [17] have
been described during pregnancy and up to 12 months
post-partum in normotensive pregnant primigravida
compared with multigravida, without a difference in
blood pressure being observed. It is possible that these
changes are more pronounced in women that develop hypertension, resulting in a relative elevation of blood
pressure in primigravida that persists, albeit to a lesser
extent, for at least 6 months post-partum. An alternative
explanation is that higher post-partum blood pressures
may reflect higher normal blood pressure in this group
prior to pregnancy.

Nearly half of the multigravid women studied by us
reported that they had previously suffered pre-eclampsia.
Only one subject reported having a different partner
from her last pregnancy, making it unlikely that altered
paternity was contributing significantly to pre-eclampsia
in the multigravid women. Multigravid women with
recurrent pre-eclampsia had similar SBP values to multi-
gravida who had pre-eclampsia for the first time, perhaps
suggesting that in this group a previous normotensive
pregnancy was no more protective in terms of developing
hypertension than a previous pregnancy associated with
pre-eclampsia.

A number of biochemical and haematological para-
eters used for clinical diagnosis were measured ante-
partum. Although the levels of alkaline phosphatase were
higher than the normal range for this enzyme, there was
no difference between primigravida and multigravid.

Figure 3 Comparison of lymphocyte count area under the
curve for primigravid (●) and multigravid (■) women with
pre-eclampsia

PP, post-partum. P < 0.01 for comparison between primigravid and multigravid
women.
However, aspartate aminotransferase was significantly elevated in primigravida before delivery, suggesting that these women had greater hepatic dysfunction. Plasma creatinine and proteinuria were similar in the two groups, suggesting a similar level of renal impairment. Antenatal platelet counts were similar in the two groups. Only three women in each group had platelet counts of less than $150 \times 10^9$/litre, suggesting that platelet consumption was not a marked feature of pre-eclampsia in these women. Haematocrit was similar in the two groups, suggesting that plasma volume was affected to a similar extent in primigravida and multigravida. The levels of all these biochemical and haematological parameters were normalized post-partum and were not different between the groups, again suggesting that underlying disease was not present in the multigravida. Our study confirms observations in a group of 825 women with both mild and severe pre-eclampsia who presented at a later stage of gestation, and in whom an increased incidence in primigravida of severe hypertension and liver disease was also observed [18].

We were unable to find evidence for differences in biochemical markers of endothelial dysfunction in relation to parity, although the levels of 2,3-dinor-6-oxo-PGF$_{1\alpha}$ were reduced in pre-eclampsia and levels of plasma endothelin-1 were elevated compared with those in normotensive pregnant controls measured by us in previous studies [7]. Some studies have shown that lipid metabolism is altered prior to the onset of clinical symptoms in women who develop pre-eclampsia [19,20], suggesting that lipids may be important in the pathophysiology of the syndrome. Our study measured plasma triacylglycerols and total, LDL and HDL cholesterol, but found them to be unaffected by parity. The levels of triacylglycerols in the women we studied were raised compared with levels we have observed previously in normal pregnancy, similar to those of proteinuric pre-eclamptics studied previously by us [12,21]. This contrasts with the study of Deslypere et al. [22] in normal pregnant women studied within 48 h of delivery, who reported that triacylglycerol and LDL levels were increased in multipara. Differences in body mass index between the parous groups in the two studies might account for these discrepancies.

Although leucocytes are not assessed in the clinical diagnosis of pre-eclampsia, they may be important in the pathophysiology of the disease because of their ability to contribute to endothelial dysfunction when activated by released cytokines or cytotoxic substances. A number of studies in women with pre-eclampsia have shown that neutrophils are activated compared with normal pregnancy [11,23,24], raising the possibility that they may contribute to endothelial dysfunction. In the present study, marked elevations in monocyte, basophil and lymphocyte counts were observed in the pre-eclamptic primigravid women compared with the multigravida before delivery, with lymphocyte counts remaining elevated for up to 6 months post-partum. The effect of parity on monocyte, basophil and lymphocyte counts appears to be specific to women with pre-eclampsia, as we have not found such differences in primigravid women who had normal pregnancies (results not shown).

An inappropriate immune response to foreign antigens has been postulated as the cause of the pre-eclamptic syndrome in primigravid subjects [6,25]; however, evidence to support this hypothesis is weak. One could speculate that if basophils, monocytes and lymphocytes are activated to a different extent in primigravida, then higher counts of these cell types in primigravida may, in part, explain the differences in severity. Whether the changes in white cell count represent an inflammatory response to endothelial, placental or other organ damage in pre-eclampsia, or indicate a more significant immune disturbance affecting vascular and placental function, remains to be determined. The difference in lymphocyte counts which persists for 6 months after delivery may be due to an ongoing inflammatory response in primigravida, or may reflect an underlying immunological disturbance that existed in these women prior to pregnancy. Further studies are needed to confirm these findings, and to clarify the role, if any, of lymphocytes, monocytes and basophils in the cause-and-effect chain of pathophysiological changes in pre-eclamptic primigravida.

In conclusion, the elevated SBP and raised aspartate aminotransferase activity observed in primigravida with pre-eclampsia suggest a more severe form of the syndrome compared with that in multigravida. The lack of differences in birthweight and other biochemical and endothelial markers of severity of pre-eclampsia do not suggest a different pathophysiology; however, the persistently higher white cell counts in the primigravid pre-eclamptics are of interest, and may reflect differences in immune responses between the two groups. We suggest that studies investigating the pathophysiology of pre-eclampsia should include multipara as long as there is adequate post-partum follow-up to exclude underlying disease.

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