RENAL PROSTAGLANDINS E$_2$ AND F$_{2\alpha}$ IN NORMAL PREGNANCY AND IN PREGNANCY WITH HYPERTENSION

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Introduction

The occurrence of hypertension during pregnancy remains a major problem, as regards both the understanding of the pathophysiological mechanisms involved and the choice of proper management. Hypertension can be one of the criteria of gravidic nephropathy (‘toxaemia’) or may be the sole manifestation requiring treatment. The pathogenesis of gravidic nephropathy seems to be related to a decrease in uterine blood flow, with development of placental ischaemia. Isolated hypertension in pregnancy, usually occurring before the 24th week, is often related to hypertensive disease which is not dependent on the pregnancy. However this hypertensive state, in some of the patients, rapidly disappears following delivery. This entity is considered by some authors to be the first manifestation preceding the development of essential hypertension years later [1].

Recently, abnormalities in renal prostaglandins (PGs) synthesis have been described in animal models of hypertension [2] and in human essential hypertension [3]. In our previous work [4] we found a decrease in urinary PGE$_2$ and/or an impaired PGE$_2$/PGF$_{2\alpha}$ ratio in essential hypertension. We suggested that an increased activity of the enzyme PGE$_2$-9-ketoreductase could explain those findings [4]. We therefore measured the urinary excretion of PGE$_2$ and PGF$_{2\alpha}$, which reflect the renal synthesis of these substances [2], in women with hypertension in pregnancy. The results were compared with those obtained in a control group of normal pregnant women and with those found in non pregnant normal and hypertensive women.

Material and methods

Four groups of subjects were studied. Group I comprised 15 normal non pregnant women (NW) aged 24 to 45 years (mean 34). Group II comprised 13 women with essential hypertension (HW) aged 18 to 46 years (mean 33). In the third group there were 24 women with normal pregnancy (NP) aged 18 to 38 years (mean 28). The fourth group consisted of 14 women with hypertension in pregnancy (HP)
aged 24 to 40 years (mean 30). All pregnant women were studied during the last trimester of their pregnancy (week 24 to 40).

Blood pressure was measured three times and the mean of such measurements was used for calculation of the mean arterial pressure (MAP) according to the formula $\text{MAP} = \text{diastolic blood pressure} + \frac{1}{3}$ of the pulse pressure. Hypertension was defined as blood pressure $\geq 140\text{mmHg}$ systolic and/or $\geq 90\text{mmHg}$ diastolic, or $\geq 107\text{mmHg}$ MAP.

Essential hypertension was diagnosed after extensive investigation comprising urinalysis, creatinine clearance, blood and urinary electrolytes and urinary vanyl-lilmandelic acid. Rapid sequence intravenous pyelography (IVP) and $^{99m}\text{Te-DTPA}$ renal scan were performed in all subjects (before or after pregnancy in the pregnant subjects). In all HP patients hypertension was found before the 24th week of pregnancy, and in some of them it was known before pregnancy. No patients with proteinuria were included in the study. All subjects were without any treatment for at least two weeks before the study and were asked to refrain from sexual intercourse for 48 hours prior to the urine collections.

Twenty four hours urine collections were obtained while the subjects were on an ad libitum diet. Urine was collected under refrigeration and samples were kept at $-20^\circ\text{C}$ until assayed. In addition to PGs measurements, urine was assayed for sodium (Na), potassium (K), creatinine and protein excretion. Na and K were measured by flame photometry. Creatinine and protein were measured with a Technicon Autoanalyzer. Prostaglandins were measured by a radioimmunoassay as previously described [5]. Creatinine clearance in the pregnant women was calculated and corrected to $1.73m^2$ according to the body surface area before pregnancy. Results are expressed as mean ± SEM and were compared by means of the Student’s t-test for unpaired results.

**Results**

Urinary PGE$_2$ was $1025 \pm 101$ng/24 hours in NP women. This was significantly greater than in NW (p < 0.01). PGF$_{2\alpha}$ excretion was also significantly greater than in NW (2276 ± 203 versus 1043 ± 229ng/24 hours, p < 0.01). The PGE$_2$/PGF$_{2\alpha}$ ratio (E/F ratio) was significantly lower in NP than in NW (0.49 ± 0.05 versus 0.88 ± 0.28, p < 0.05). PGE$_2$ excretion was even greater in HP: 1759 ± 220ng/24 hours. This value was significantly higher than that of NP (p < 0.01). The same was true of PGF$_{2\alpha}$ excretion: 5149 ± 759ng/24 hours (p < 0.01 when compared to NP). The E/F ratio in this group was 0.33 ± 0.05 which differs significantly from the value found in NP (p < 0.02). In contrast, PGE$_2$ excretion was somewhat lower in HW as compared to NW, while PGF$_{2\alpha}$ was slightly higher. The E/F value was lower in HW than in NW. However, these differences were not significant statistically (Table I).

Diuresis was significantly higher in pregnant than in non pregnant women, and this was true for both NP and HP. There was no statistically significant difference in Na excretion between the four groups. K excretion was similar in NW, HW and NP, but was significantly increased in HP (p < 0.02, when compared with NP) (Table II).

When HP were compared to NP, no significant differences in age, gestational
### TABLE I. Prostaglandins excretion in the four groups

<table>
<thead>
<tr>
<th></th>
<th>NW</th>
<th>HW</th>
<th>NP</th>
<th>HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>13</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>PGE$_2$ (ng/24 h)</td>
<td>509 ± 80</td>
<td>452 ± 80</td>
<td>1025 ± 101*</td>
<td>1759 ± 220†</td>
</tr>
<tr>
<td>PGF$_{2\alpha}$ (ng/24 h)</td>
<td>1043 ± 229</td>
<td>1099 ± 135</td>
<td>2276 ± 203*</td>
<td>5149 ± 759†</td>
</tr>
<tr>
<td>E/F ratio</td>
<td>0.88 ± 0.28</td>
<td>0.48 ± 0.08</td>
<td>0.49 ± 0.05‡</td>
<td>0.33 ± 0.05§</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM
When compared with NW: * = p < 0.01, ‡ = p < 0.05
When compared with NP: † = p < 0.01, § = p < 0.02

### TABLE II. Diuresis and electrolyte excretion

<table>
<thead>
<tr>
<th></th>
<th>NW</th>
<th>HW</th>
<th>NP</th>
<th>HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>15</td>
<td>13</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Diuresis (ml/24 h)</td>
<td>1306 ± 115</td>
<td>1049 ± 126</td>
<td>1604 ± 63*</td>
<td>1675 ± 85†</td>
</tr>
<tr>
<td>Urinary Na (mmol/24 h)</td>
<td>130 ± 22</td>
<td>179 ± 22</td>
<td>139 ± 8.9</td>
<td>176 ± 13</td>
</tr>
<tr>
<td>Urinary K (mmol/24 h)</td>
<td>63 ± 18</td>
<td>63 ± 6</td>
<td>57 ± 4</td>
<td>71 ± 5‡</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM
* p < 0.01 when compared with NW
† p < 0.01 when compared with HW
‡ p < 0.02 when compared with NP

### TABLE III. Comparison of normal and hypertensive pregnant women

<table>
<thead>
<tr>
<th></th>
<th>NP</th>
<th>HP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Range</td>
<td>18 – 38</td>
<td>24 – 40</td>
</tr>
<tr>
<td>Week of pregnancy</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Range</td>
<td>24 – 40</td>
<td>24 – 39</td>
</tr>
<tr>
<td>% increase in body weight*</td>
<td>20.7 ± 2.2</td>
<td>18.7 ± 2.1</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>82 ± 2</td>
<td>112 ± 2</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73m$^2$)†</td>
<td>143 ± 5</td>
<td>154 ± 10</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM
* increase in body weight with respect to pre-pregnancy weight
† corrected according to pre-pregnancy body surface area
week or percent increase in body weight were noted. Creatinine clearance was higher in HP than in NP, but this was not statistically significant (Table III).

**Discussion**

In this study, a greatly increased urinary excretion of PGE₂ and PGF₂α was found in normal pregnant as compared with non pregnant women. In the non pregnant subjects with essential hypertension PGE₂ excretion was lower than in normal subjects (although in the small groups studied this difference was not statistically significant). In contrast, the pregnant women with hypertension had greatly increased PGE₂ and PGF₂α levels. In both pregnant groups the E/F ratio was significantly lower than in normal women. This ratio was even lower in the HP group, as compared with NP.

PGE₂ has been found to be elevated in the blood of pregnant women [6]. However, PGE₂ injected systemically is not found as such in the urine [2] and it appears unlikely that the increase in urinary PGs is due to their clearance from the blood. In this respect, our findings confirm and extend those of Bay et al who also found increased PGE₂ in the urine of pregnant women [6]. The increase of both PGs in pregnancy suggests an increase in production at the level of the first steps of their biosynthesis (increase in phospholipase A or in cyclo-oxygenase activity) or a decrease in catabolism. In addition, the decreased E/F ratio suggests that the activity of PGE₂-9-ketoreductase may also be increased [2, 5].

Many hormonal factors, peculiar to pregnancy, could contribute to the increased PGs synthesis. Angiotensin II and the antidiuretic hormone (ADH), both of which can increase phospholipase A activity [2], are increased in pregnancy. Oestrogen and progesterone levels are also increased in pregnancy and have been shown to increase PGE and F release from the uterus [7]. A similar action on the kidney is conceivable, particularly as an oestrogen receptor has been detected in renal tissue [8]. DOCA, also elevated in pregnancy, could influence renal PGs synthesis, as has been demonstrated in DOCA-salt treated animals [9]. Finally, renal kallikrein has been shown to be increased in pregnancy [10]. An increased activity of the kallikrein-kinin system could increment renal PGs synthesis [2, 5].

Of great interest is the finding of a decreased E/F ratio in both normal and hypertensive pregnant women. This ratio, which is mainly governed by the activity of the enzyme PGE₂-9-ketoreductase, could be of physiological significance with respect to tubular Na handling [5]. A low E/F ratio has been described in animals fed a high Na diet, while we have observed the E/F ratio to increase during Na restriction in man [5]. Thus, a decreased E/F ratio in pregnant women, even with elevated absolute levels of PGs, is not surprising, as pregnancy is undoubtedly a Na retaining state.

It must be noted that all the above mentioned humoral changes, while proposing several possible mechanisms for the changes in PGs synthesis observed in normal pregnancy, are not likely to explain the extremely elevated PGs levels in hypertensive pregnant women. To our knowledge, no differences in the various hormones have been described between normal and hypertensive pregnant women. On the other hand, the lowered E/F ratio present in hypertensive, as compared to
normal pregnant women, is in accordance with the findings described by us in essential hypertension [4].

In conclusion, renal prostaglandins E$_2$ and F$_{2\alpha}$ are increased in pregnancy, although PGF$_{2\alpha}$ is relatively higher than PGE$_2$. Several humoral and volume-related changes, peculiar to pregnancy, could contribute to the increase in PGs. In pregnant women with hypertension, the renal PGs are still further increased, with the E/F ratio even lower. The reason(s) for the difference between normal and hypertensive pregnant women are presently unknown and are the subject of further investigation.

Acknowledgment

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References

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Open Discussion

STRUYVENBERG (Chairman) Have you re-studied the groups who were pregnant after the pregnancy, and what happened to them?

BERNHEIM This is a prospective study and we are beginning to see these patients after pregnancy. I hope that we shall be able to evaluate which patients will develop essential hypertension.