Plasma Prostaglandins in Pregnancy

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Plasma prostaglandins were determined by radioimmunoassay in 92 pregnant and 14 nonpregnant women. There was significant elevation of PGA-like material in the first trimester of pregnancy (1744 pg/ml) over that seen in nonpregnant women (576 pg/ml) with continuation of that elevation in the second and third trimesters. No significant difference existed among PGE levels of the nonpregnant group (251 pg/ml) and the first two trimesters of pregnancy (384 pg/ml and 294 pg/ml); the PGE level of the third trimester group (443 pg/ml) was significantly elevated over that of the nonpregnant group. PGF levels remained constant during all trimesters (135 pg/ml, 144 pg/ml, and 130 pg/ml) but exhibited plasma concentrations significantly higher than the nonpregnant group (78 pg/ml). Potential role(s) of prostaglandins as mediators of cardiovascular and renal changes of pregnancy are discussed.

Pregnancy is accompanied by alterations in the function of many organ systems. The most dramatic physiologic changes occur in the cardiovascular and renal systems, where increases of 30–40% are seen in measurements such as cardiac output, plasma volume, renal blood flow, and glomerular filtration rate. Both systems exhibit augmented function early in pregnancy, long before differences could be attributed to the presence of an arteriovenous shunt in the placenta, enormous steroid output, or the need for excretion of massive amounts of metabolites. In many respects, the physiologic changes of pregnancy resemble the effects produced by the administration of prostaglandins, especially those of the A and E series. Since genital structures are particularly potent sources of prostaglandins, and hormonal state appears to influence the type as well as the quantity of the prostaglandins detected, one could postulate that the cardiovascular and renal alterations occur in response to prostaglandins elaborated during pregnancy.

Evaluation of this postulate on the basis of existing data is difficult. Some of the studies of prostaglandins in pregnancy have been done with relatively insensitive or nonspecific bioassays and other studies involved radioimmunoassay employing serum samples which have since been shown to contain prostaglandins generated during the clotting process. Consequently, the following study has been carried out to define the plasma levels of prostaglandins observed in normal pregnancy, and to determine if there are changes in the levels of circulating prostaglandins which could account for the cardiovascular and renal adjustments during pregnancy.

MATERIALS AND METHODS

The sample population consisted of women with medically uncomplicated pregnancies who were seen for routine prenatal care and women who were seen for early termination of pregnancy at the Department of Obstetrics and Gynecology at the University of Iowa Hospitals and Clinics. The duration of gestation was computed for each pregnant woman from her menstrual history and verified, where possible, by the pathologist's examination of the products of conception. Samples were obtained from a total of 92 pregnant women. For the purpose of analysis the samples were grouped according to the trimesters of pregnancy: Trimester 1, 1–13 weeks; Trimester 2, 15–26 weeks; and Trimester 3, 26–40 weeks. The study also included a control population of 14 nonpregnant women from whom samples were taken every other day throughout their menstrual cycle. No samples were obtained from women who had taken drugs other than iron and vitamins within the preceding 24 hours.

Sample preparation and radioimmunoassay of prostaglandin E (PGE) and prostaglandin F (PGF) were done according to the methods of Van Orden et al. The assay for prostaglandin A (PGA)-like material (PGA, PGA, and 13, 14-dihydro PGA) was performed as described in the accompanying paper. Samples were assayed in duplicate at one volume with a third determination at a larger volume. Results were corrected for aliquot size and procedural recovery. The coefficient of variation was calculated for the three values obtained for each unknown; data were included in the study only if the coefficient of variation was less than 20%. For this reason, the number of samples in each of the prostaglan-
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![Graph showing distribution of plasma A-like prostaglandin values in pregnancy.]

Fig 1. Distribution of plasma A-like prostaglandin values in pregnancy.

The mean analyses varied (PGA-like material, N = 88, PGE, N = 72, PGF, N = 83).

The mean values and standard errors of the means (SEM) were then calculated for levels of PGA-like material, PGE, and PGF for both the nonpregnant women and the women in each of the trimesters of pregnancy.

For each of the prostaglandins, one-way analyses of variance were performed to determine differences among the means of the nonpregnant control group and the means of each of the pregnancy trimesters. When there was a significant overall F-test, Tukey's multiple comparison test was then used to compare all possible pairs of the means of the 4 groups.

ANALYSIS OF DATA

Figure 1 shows the distribution of the values for PGA-like material observed in 88 pregnant women. The mean ± SEM for A-like prostaglandins for nonpregnant women and women in each trimester of pregnancy are shown in Table 1. The mean value for PGA-like material was 576 pg/ml in nonpregnant females. There was a significant elevation in the first trimester (1744 pg/ml, P < 0.001) with a continuation of that elevation in the second and third trimesters (1687 and 1515 pg/ml). No significant difference among mean values for the three trimesters of pregnancy was shown.

Figure 2 shows the distribution of PGE values for 72 pregnant women. The mean ± SEM PGE values of the nonpregnant and pregnant women are shown in Table 1. A significant difference did not exist among the mean PGE value of the nonpregnant group (251 pg/ml) and the means of the first two trimesters of pregnancy (384 pg/ml and 294 pg/ml). The mean PGE level of the third trimester of pregnancy (443 pg/ml) was significantly elevated over the mean PGE level of the nonpregnant group (P < 0.05); however, it was not significantly greater than the first and second trimester values.

The distribution of prostaglandin F values for 83 pregnant women are shown in Figure 3. The mean ± SEM PGF levels of the nonpregnant and pregnant groups are shown in Table 1. Prostaglandin F values were remarkably constant during pregnancy with means ranging from 130–144 pg/ml and were significantly elevated above the mean value of the nonpregnant group (78 pg/ml; P < 0.001).

Correlations were sought between the PGA-like material, PGE, and PGF values in pregnant women for whom all three values were available. No relations were identified between trimester of pregnancy and the three types of prostaglandins.

DISCUSSION

The study of 92 pregnant women has shown a significantly elevated level of PGA-like material, PGE, and PGF when compared to the levels observed in nonpregnant controls. The A-like prostaglandins showed the most dramatic increase over nonpregnant values with a threefold elevation occurring in the first trimester and persisting until term. The identity of the A-like material cannot be specified since PGA1, PGA2, and 13, 14-dihydro prostaglandin A all react with the antiserum used. Although prostaglandin data obtained by gas chromatography-mass spectrometry reasonably exclude PGA1 and PGA2 as major A-like components of peripheral blood in the nonpregnant woman,12,13 there have been no comparable studies of pregnancy plasma. Nevertheless, a consideration of PGA metabolism and renal hemodynamic changes in pregnancy predict that the A-like material present in pregnant plasma is also 13, 14-dihydro PGA. Attalah et al have shown that the kidney

<p>| Table 1. The Concentrations (Mean ± SEM) of Peripheral Plasma Prostaglandins for Nonpregnant Women and Women in Each of the Trimesters of Pregnancy |
|----------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>PGA</th>
<th>PGE</th>
<th>PGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpregnant</td>
<td>N</td>
<td>Mean (pg/ml) ± SEM</td>
<td>N</td>
</tr>
<tr>
<td>Trimester I</td>
<td>11</td>
<td>576 ± 51</td>
<td>14</td>
</tr>
<tr>
<td>Trimester II</td>
<td>18</td>
<td>1744 ± 188</td>
<td>13</td>
</tr>
<tr>
<td>Trimester III</td>
<td>28</td>
<td>1687 ± 319</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>1515 ± 234</td>
<td>41</td>
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</table>

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is capable of extensive conversion of infused PGA (at doses up to 50 μg) to its metabolites on a single pass through the organ, and have identified the cortex, rather than the medulla, as the degradative site.14 Combining this information with the fact that renal blood flow and glomerular filtration rate (ie, cortical flow) are increased up to 50% early in pregnancy,1 one can hypothesize that A prostaglandins should be more efficiently cleared from blood in the pregnant than in the nonpregnant female. If the increase in degradative activity predicted by these basic experiments actually takes place in the pregnant woman, any increase in production of PGA would be manifested as an increase in metabolite. Whether the A-like material is a primary prostaglandin or a metabolite, a physiologic effect should be expected, since PGA₄, PGA₆, and the 13, 14-dihydro PGA all exhibit vasoactivity.18 Thus, the decreased peripheral resistance and increased cardiac output seen early in pregnancy, which are also typical effects of the PGAs, may be the physiologic response to the high levels of PGA-like substances shown in this group of pregnant women.

Prostaglandin F₃α levels show a pattern similar to that of the PGA-like material. There is a significant elevation with the occurrence of pregnancy and a maintenance of the elevated levels until term. The elevated levels seen in this study could be due to increased production, decreased degradation, or increases in production exceeding degradation. The latter explanation appears to be the case, since Hamberg has shown that pregnancy is accompanied by a progressive increase in the urinary output of PGF metabolites,18 and has demonstrated elevated pulmonary dehydrogenase activity in pregnancy.17 Because any discrepancy between production and degradation of PGF would produce an alteration in plasma levels, the magnitude of the change in PGF gives a hint about the balance maintained between these processes. The fact that we see only a 70-pg elevation in plasma PGF during pregnancy, while Hamberg reports 40-μg increases in urinary metabolites, indicates that production and degradation of PGF in pregnancy are balanced within remarkably close limits. Furthermore, the enormous output of urinary metabolites indicates a very rapid turnover of the F prostaglandins in pregnancy. In such a situation, plasma levels of PGF would have limited significance and one would predict that study of plasma or urinary metabolites would show greater correlation with physiologic responses.

The pattern of PGF in pregnancy differed from that seen for A-like material and PGF. There was no significant increase in PGF until the third trimester when levels were elevated by 31%. Since prostaglandins E and F are metabolized by the same pulmonary enzyme sys-

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Fig 2. Distribution of plasma prostaglandin E values in pregnancy.

Fig 3. Distribution of plasma prostaglandin F₃α values in pregnancy.
generation of PGE. Of the two studies, Gimbrone's work, which showed that angiotensin II would prompt the generation of PGE by endothelium in tissue culture, is of greater interest in the context of the present study. Elevations of angiotensin II without increases in blood pressure are well documented in pregnancy, and infusion studies suggest that the pregnant woman is in a state of tachyphylaxis with respect to angiotensin II.1,34 Also Gryglewski and Oecetkiewicz28 showed in animal studies that the development of angiotensin II tachyphylaxis is prevented by prostaglandin synthesis inhibitors. Taken as a group, these studies may indicate that augmented production of angiotensin II is a primary change in pregnancy, and that generation of PGE occurs in vessels to prevent a hypertensive state. The parallel between the pattern of angiotensin II increases in pregnancy and the increases which we have shown for PGE is striking, and suggests that the study of plasma angiotensin II and prostaglandin E production in normal and hypertensive pregnancy would be a fruitful area of research.

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