Reproductive hormones and blood pressure during pregnancy

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The mechanisms involved in cardiovascular changes during human pregnancy and the complicated aetiology of gestational hypertension are unclear. Reproductive hormones have known effects on the cardiovascular system in the non-pregnant state and in animal systems, but their effects in human pregnancy are uncertain. In this study of pregnant women, the effects of serum concentrations of relaxin, progesterone and oestradiol on arterial blood pressure were studied. Higher serum concentrations of progesterone and relaxin, but not oestradiol, in early pregnancy were related to lower mean systolic blood pressures in the second and third trimesters. No relationship was found between hormonal concentrations and diastolic blood pressures. However, women with a diastolic blood pressure of \( \leq 90 \text{ mmHg} \) in late pregnancy showed statistically significant lower relaxin concentrations in early pregnancy in comparison with women whose diastolic blood pressure was \( \geq 90 \text{ mmHg} \). In a multivariate analysis, the mean systolic blood pressure \((P < 0.0001)\) and serum relaxin \((P < 0.01)\) in early pregnancy, but not progesterone, were independently related to systolic blood pressure in late pregnancy. The results support previous experimental and clinical studies. The effect of relaxin may be explained by a possible vasodilatatory action seen in animal studies and appears to be moderate.

Key words: blood pressure/oestradiol/pregnancy/progesterone/relaxin

Introduction

There are cardiovascular changes during pregnancy where the mechanisms involved are unclear. In human pregnancy there is an increase in cardiac output and blood volume and a decrease in peripheral vascular resistance (Duvekot and Peeters, 1998). Reproductive hormones have known effects on the cardiovascular system in the non-pregnant state and in laboratory systems, but the effects in human pregnancy are uncertain. Oestrogen has been suggested to have both functional and structural haemodynamic effects via a transient vasodilating effect and through increased aortic compliance in post-menopausal women (Gilligan et al., 1995). Progesterone has been reported to reduce blood pressure in hypertensive subjects (Rylance et al., 1985) and to induce vascular relaxation (Omar et al., 1995).

The polypeptide hormone, relaxin, is a member of the insulin growth factor family. Relaxin in serum is produced predominantly by the corpus luteum of the ovary (Sherwood, 1994). In women a peak value is reached early in the second trimester followed by a decline to a stable value at \( \approx 50\% \) of the peak (Kristiansson et al., 1996). The placenta also produces relaxin, where it may have a paracrine action without raising serum relaxin concentrations (Bryant-Greenwood et al., 1994). Relaxin is best known for its connective tissue remodelling effects on the female reproductive system (Sherwood, 1994). However, additional effects in other organs and systems are suggested. In several animals and tissues, relaxin has been shown to cause powerful vasodilatation (Bigazzi et al., 1986; Danielson et al., 1999).

In Sweden, all pregnant women are offered free maternity health care during pregnancy at local antenatal clinics run by the County Health Care Board. More than 95% of women make use of this offer, which makes this organization suitable for epidemiological studies during pregnancy. The present study was designed to evaluate changes of systolic and diastolic blood pressure in a healthy population during pregnancy and to study the possible relationship between the changes and the reproductive hormones, relaxin, oestrogen and progesterone.

Materials and methods

In 1991, all pregnant women living in two districts (population 23 350) of the city of Sundsvall (population 93 800), Sweden, were identified through check-ups at the antenatal clinics in the city and its surroundings, at practising obstetricians’ offices and at the outpatient clinic at the local hospital. All women attending during early
pregnancy in the year 1991 were sampled for this study. A total of 227 pregnant women fulfilled this sampling criterion, of which 222 women attended the antenatal clinic that served the two districts and five women attended other antenatal clinics. The 222 women were invited to participate in the study. In all, 22 declined to participate, which left 200 (88.1%) women of European origin in the final study population.

The mean age of the women studied was 27.9 years [95% confidence interval (CI) 27.2–28.5 years] at the first visit to the antenatal clinic. Of them 41% were pregnant for the first time, 37% for the second time and 22% for the third time or more. All women were apparently healthy and none of them were taking continuous medication at the time of inclusion.

During follow-up, 10 women left the study because of spontaneous miscarriage, two women declined further participation and one woman moved from the area. Permission for this study was obtained from the Research Ethics Committee of the University of Umeå, Sweden.

The medical care programme of the antenatal clinic included scheduled appointments with a physician or a midwife. The appointments with the midwife were once a month up to week 28, every second week until week 36 and thereafter weekly. The appointments with the physician were prior to week 12 of pregnancy and at about week 36. The duration of pregnancy was confirmed by ultrasound examination and was registered as completed weeks of gestation.

The arterial blood pressure in the brachial artery was measured by indirect means using a mercury sphygmomanometer with a cuff of adequate size. Auscultatory blood pressure measurements utilising the onset of the first (systolic) and fifth (diastolic) sounds of Korotkov were taken in the right arm with the woman seated after 5 min of rest and registered to the nearest 5 mmHg. Blood pressure was taken and registered by the midwife at each appointment with the midwife or physician.

At each visit to the physician, the women completed a questionnaire where information was obtained on smoking habits and earlier obstetric history regarding the number of previous pregnancies and deliveries. Weight, height and smoking habits were recorded.

Five visits for blood sampling were scheduled at gestational weeks 8, 16, 20, 28 and 36. Actual visits occurred within 4 weeks of these dates, at weekly intervals 6–12, 13–17, 18–22, 24–31 and 32–38 respectively. The blood samples were centrifuged immediately after sampling and the serum was stored at –70°C until analysis.

Hormone assays
Serum concentrations of relaxin were determined by a non-competitive double-antibody enzyme-linked immunosorbent assay based on purified antibodies raised against a recombinant human relaxin (hRlx-2) as described previously (Lucas et al., 1989). The lowest detectable concentration was 20 ng/l and the intra- and inter-assay coefficients of variation were 5 and 12% respectively. Serum concentrations of oestradiol and progesterone were determined by radioimmunoassay. The intra- and inter-assay coefficients of variation were 7 and 8% for oestradiol, and 9 and 10% for progesterone respectively. All serum samples were analysed blindly in duplicate.

Statistical analyses
Data were analysed with the Statistical Analysis System program package. Possible relationships between continuous data were tested with Pearson’s correlation coefficients and between continuous and ordinal data with Spearman’s correlation coefficients. In the analysis of serial measurements of blood pressure the mean of blood pressure measurements in five different time periods of gestation, i.e. one blood pressure value for each woman per gestation period, was used. The weekly intervals chosen were 8–12, 13–17, 18–23, 24–31 and 32–38 respectively. The paired t-test was used when comparing the different blood pressures. For multivariate analysis the general linear model was used. Only two-tailed tests were used. P < 0.05 was considered to be statistically significant.

Results
The characteristics of the women in the study are shown in Table I. The mean number of measurements of blood pressure at the weekly intervals 8–12, 13–17, 18–23, 24–31 and 32–38 was for each woman 1.1, 1.1, 1.3, 3.0 and 4.5 respectively. During the pregnancy period, the mean number of measurements was 10.8 (95% CI 10.6–11.0).

Mean blood pressure
Systolic and diastolic blood pressures during pregnancy are shown in Figures 1 and 2 respectively. The mean systolic blood pressure continued to rise during pregnancy, with the highest increase of 2.1 mmHg between the weeks 8–12 and 13–17 (P < 0.01). Thereafter the increases between each of the weekly intervals were smaller and not statistically significant. The overall increase of mean systolic blood pressure from weeks 8–12 to 32–38 was 3.3 mmHg, which was 2.8% above the initial level (P < 0.0001). The mean systolic blood pressures at the different weekly intervals were highly inter-correlated (0.46 < r < 0.74, P < 0.0001) and the mean systolic blood pressure at 8–12 weeks was most closely correlated with mean systolic blood pressure at weeks 32–38 (r = 0.56, P < 0.0001).

The mean diastolic blood pressure showed a statistically significant (P < 0.001) decrease of 2.7 mmHg from 69.6 mmHg at weeks 8–12 to the nadir of 66.9 mmHg at weeks 18–23. From this lowest level, the diastolic blood pressure increased by 6.5 mmHg to 73.4 mmHg at weeks 32–38 (P < 0.0001). The overall increase of diastolic blood pressure over the study period was 3.8 mmHg that was 5.4% above the initial level (P < 0.0001). The mean diastolic blood pressures at the different weekly intervals were highly inter-correlated (0.40 < r < 0.74, P < 0.0001). The mean diastolic blood pressure at weeks 8–12 showed the strongest correlation to mean diastolic blood pressure at weeks 32–38 (r = 0.54, P < 0.0001).

Mean systolic blood pressure and serum markers
Both serum progesterone and relaxin concentrations at weeks 8–12 showed a weak, but statistically significant, negative correlation with mean systolic blood pressures at weekly intervals (weeks 18–23). The correlation coefficients and P values for relaxin at the three time intervals were r = –0.17, P = 0.02 (weeks 18–23), r = –0.18, P = 0.02 (weeks 24–31) and r = –0.22, P = 0.005 (weeks 32–38) and for progesterone r = –0.25, P = 0.001 (weeks 18–23), r = –0.22, P = 0.003 (weeks 24–31) and r = –0.17, P = 0.03 (weeks 32–38). The same tendency was shown with regard to mean systolic blood pressures at weekly intervals (weeks 8–12 and 13–18), although this was not statistically significant. Progesterone and relaxin concentrations measured later in pregnancy showed no association with mean systolic blood pressure.
Table I. Characteristics of the women in the study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Mean (SD) or Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>200</td>
<td>27.9 (4.6) 18–42</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>187</td>
<td>166.2 (5.7) 147–184</td>
</tr>
<tr>
<td>Weight in early pregnancy (kg)</td>
<td>188</td>
<td>63.7 (8.7) 46.9–104.1</td>
</tr>
<tr>
<td>BMI in early pregnancy (kg/m²)</td>
<td>187</td>
<td>23.0 (2.9) 18.2–36.0</td>
</tr>
<tr>
<td>Weight gain (kg)</td>
<td>186</td>
<td>12.8 (4.6) 0.2–30.8</td>
</tr>
<tr>
<td>Relaxin (ng/l) at weeks 8–12</td>
<td>167</td>
<td>896.5 (431.3) 180–2550</td>
</tr>
<tr>
<td>Progesterone (nmol/l) at weeks 8–12</td>
<td>170</td>
<td>70.9 (23.5) 27–152</td>
</tr>
<tr>
<td>Oestradiol (nmol/l) at weeks 8–12</td>
<td>170</td>
<td>3.65 (2.25) 0.28–17.1</td>
</tr>
<tr>
<td>Nulligravid</td>
<td>194</td>
<td>80 (41%)</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>194</td>
<td>116 (60%)</td>
</tr>
<tr>
<td>Uniparous</td>
<td>194</td>
<td>60 (31%)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>194</td>
<td>18 (9%)</td>
</tr>
<tr>
<td>Current cigarette smokers</td>
<td>181</td>
<td>47 (26%)</td>
</tr>
</tbody>
</table>

BMI = body mass index.

Mean systolic blood pressure and other factors

Increasing parity was weakly and negatively associated with mean systolic blood pressure during pregnancy (−0.15 < r < −0.19, P < 0.05) except with that at weeks 32–38. In addition, weight gain during pregnancy showed a positive correlation to mean systolic blood pressure at weeks 32–38 (r = 0.18, P = 0.01). There was no statistically significant relationship between systolic blood pressure and the total number of blood pressure measurements, the number of previous pregnancies, age, cigarette smoking habits or body mass index (BMI) in early pregnancy.

Mean diastolic blood pressure and serum markers

While mean diastolic blood pressure at weeks 18–23 showed a weak negative correlation with progesterone concentrations at weeks 13–17 (r = −0.16, P < 0.05), neither progesterone at other weekly intervals, nor relaxin and oestradiol concentrations, were correlated with diastolic blood pressure at any interval.

Mean diastolic blood pressure and other factors

The BMI in early pregnancy was significantly correlated with the mean diastolic blood pressure at all weekly intervals (0.16 < r < 0.22, P < 0.01). No significant relationship was shown between diastolic blood pressure and the total number of blood pressure measurements, age, smoking habits, the number of earlier pregnancies or deliveries.

At weekly intervals (weeks 32–38), 4.8% (nine out of 188) of the women had a maximum diastolic blood pressure of >90 mmHg. Within this group, the mean relaxin value at weekly intervals 8–12 was statistically significantly lower (650 ng/l) than among those with a maximum diastolic blood pressure of ≤90 mmHg (911 ng/l, P < 0.05). When these women with high diastolic blood pressure were excluded, the relationship between relaxin and systolic blood pressures as described previously remained statistically significant.

Multivariate analysis

To study the compound effect of mean systolic blood pressure in early pregnancy and the serum markers on the systolic
blood pressure in late pregnancy, a multivariate regression analysis was performed. The mean systolic blood pressure at weeks 32–38 was used as the dependent variable, and mean systolic blood pressure at weeks 8–12, serum concentrations of progesterone and relaxin at weeks 8–12 as the independent variables. Mean early systolic blood pressure ($P = 0.0001$) and serum relaxin ($P = 0.01$), but not progesterone, were independently related to the variation of systolic blood pressure in late pregnancy. The $R^2$ of the model was 0.36.

The extent of the effects of relaxin concentration and mean blood pressure measurement, at weeks 8–12, on systolic blood pressure in late pregnancy are shown in Figure 3. Women with the highest relaxin values and the lowest systolic blood pressure in early pregnancy displayed the lowest systolic blood pressures in late pregnancy and women with the lowest relaxin values and the highest systolic blood pressures in early pregnancy displayed the highest systolic blood pressures in late pregnancy.

In addition, a multivariate regression analysis, with mean diastolic blood pressure in late pregnancy as the dependent variable and with relaxin and progesterone concentrations and BMI in early pregnancy as independent variables, was performed where BMI ($P = 0.003$) was the only factor related to diastolic blood pressure. The $R^2$ of the model was 0.06.

**Discussion**

The present data suggest a hormonal influence on the haemodynamic changes in human pregnancy, since the higher concentrations of progesterone and relaxin in early pregnancy were significantly associated with lower mean systolic blood pressure in the second and third trimesters. However, causality cannot be determined from an observational study.

As expected there was a steady increase in blood pressure from early to late gestation, except for a small initial decrease of diastolic blood pressure (Contard et al., 1993; Churchill et al., 1997). However, exclusion criteria in these studies explain the slightly lower blood pressure values compared with the general population of pregnant women. In a related study, the systolic blood pressure increased by 3% during pregnancy to 118 ± 11 mmHg and the diastolic blood pressure fell initially with an overall increase by 7.7% to 72.2 ± 8.7 mmHg (Strevens et al., 1997), which agrees with the results of the present study.

There have been a few limitations of this study, including the accuracy of blood pressure measurement and the small sample size. The blood pressure was measured to the nearest 5 mmHg instead of the recommended 2 mmHg (Davey and MacGillivray, 1988) and no precaution was taken against digit preference or threshold avoidance (Steer 1999). This probably reduced the sensitivity of the study to show any but the strongest effect on blood pressure. This may explain why the known weak association of age with blood pressure during pregnancy was not statistically significant (Margulies et al., 1987). However, this may also suggest that the chance of a false positive in detecting a relationship is small.

In addition, the weak relationship between relaxin and systolic blood pressure may be because relaxin is one of several residual or redundant systems that control blood pressure in human pregnancy (Bani et al., 1998). We know of no previous study that has related relaxin concentration in pregnant women to blood pressure. In pregnancies achieved following ovum donation, an increased incidence of gestational hypertension was shown (Salha et al., 1999). This is in accordance with our results, since women pregnant following ovum donation have zero or low concentrations of relaxin detected in the circulation (Johnson et al., 1991). Furthermore, relaxin is reported to influence the changes in uterine blood flow in early pregnancy (Jauiaux et al., 1994).

The proposed relationship between early relaxin values and lower systolic blood pressure in later pregnancy may be explained by the vasodilatory action of relaxin seen in animal studies (Bigazzi et al., 1986; Danielson et al., 1999). That relaxin is involved in the regulation of blood pressure in rats is further indicated by the anti-hypertensive effect shown in female non-pregnant spontaneously hypertensive rats (St-Louis and Massicotte, 1995). Relaxin is proposed to exert the vasodilatory effect with a mediatory role of nitric oxide (Ramsay et al., 1994; Bani et al., 1998; Danielson et al., 1999) which is believed to contribute to the generalized vasodilation in normal pregnancy (Churchill and Beevers, 1999).

Why the relationship is only seen between later systolic blood pressures and early relaxin values is unclear. There are reports about the timing of the effect of relaxin suggesting that relaxin has a delayed effect. A vasodilatory effect was demonstrated in the renal circulation of conscious rats following prolonged administration of relaxin, but not following short-term infusion (Danielson et al., 1999). In addition, no effect was detected on systolic or diastolic blood pressure of human relaxin given vaginally prior to labour in a clinical trial of cervical ripening (Bell et al., 1993). In the present study, the mean systolic blood pressure showed the greatest increase during the first trimester, which may not be determined by relaxin. The lower increase during later pregnancy may be determined by relaxin in early pregnancy, as shown by the relationship between relaxin and systolic blood pressure in the present study.
Progesterone has also been reported to reduce blood pressure in hypertensive subjects (Rylance et al., 1985) and to induce vascular relaxation (Omar et al., 1995). In the present study, the effect of progesterone on the variation of systolic blood pressure could be explained by the variation in relaxin concentration, as shown in the multivariate regression analysis.

Of the present cohort, ~5% had a diastolic blood pressure of >90 mmHg and may have had gestational hypertension. This prevalence is close to the previously reported value of 6.7% for hypertensive disorders of pregnancy (Churchill and Beevers, 1999). In the present study, women with a diastolic blood pressure of >90 mmHg had significantly lower relaxin values in early pregnancy when compared with women without hypertension. However, in the whole group of women, no relationship was shown between the concentrations of relaxin and diastolic blood pressure. There may be a relationship between the concentration of relaxin in very early pregnancy, not measured in the present study, and subsequent diastolic blood pressure.

In conclusion, the hormone relaxin in early pregnancy may be involved in the haemodynamic changes during pregnancy. However the size of the effect may be moderate.

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References


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