Serum Level of Placental Growth Hormone Is Raised in Pregnancy Rhinitis

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Objective: To describe any relationship between pregnancy rhinitis and weight gain or serum levels of estradiol, progesterone, placental growth hormone, or insulinlike growth factor I.

Patients: Twenty-seven nonsmoking healthy pregnant women aged 22 to 38 years (mean age, 28 years) who had no history of respiratory allergy or chronic nasal or sinus problems volunteered to enter the study. They had no nasal complaints at entry.

Methods: Nasal patency was registered daily from early pregnancy until 1 month after delivery. Nasal and oral peak expiratory flow rates were established, and the subjective blockage was scored from 0 to 4, with 0 indicating no blockage. Serum samples were collected and weight was measured on 4 occasions during pregnancy and again at the end of the study. Pregnancy rhinitis was diagnosed if the subjective nasal obstruction score was 1 or higher every morning for at least 6 weeks immediately preceding delivery, then returned to 0 within 2 weeks and remained at 0 until the end of the study. If on any day other signs of respiratory tract infection occurred, that day was excluded.

Results: Pregnancy rhinitis was diagnosed in 5 women. These 5 women showed significantly higher levels of placental growth hormone than the women without the diagnosis. No significant difference was found between the 2 groups regarding body weight or any of the other serum levels studied.

Conclusions: Serum level of placental growth hormone is raised in pregnancy rhinitis and may be involved in its pathogeny. Pregnancy rhinitis does not significantly raise weight gain or serum levels of estradiol, progesterone, or insulinlike growth factor I.


Pregnancy rhinitis is a condition frequently encountered since the first reports almost a century ago. The prevailing theory of its cause concerns raised estrogen levels. This is based mainly on the results of Toppozada et al from biopsy studies on nasal mucosa in pregnancy and from women taking contraceptive pills. Also considered was the fact that the early high-estrogen contraceptive pills produced nasal congestion as an adverse effect. Case reports of success with nasal application of estrogen in the treatment of atrophic rhinitis also have been used as support for the estrogen theory. Although estrogen receptors have been shown to exist in nasal mucosa, other-than-direct effects of estrogen have been suggested, eg, by histamine release, cyclic adenosine monophosphate production, or a separate eosinophil receptor system. On the basis of a rather small number of patients, Bende et al favor a proposed theory of vasoactive intestinal polypeptide release by nasal nerves, causing nasal congestion during pregnancy.

Serum progesterone levels, also rising in pregnancy, may induce nasal vascular smooth muscle relaxation, resulting in local vascular pooling. This possibly also may be influenced by the raised systemic blood volume.

However, some authors believe that pregnancy rhinitis is not a specific entity, but merely a reflection of other conditions, such as stress, allergies, or rhinitis medicamentosa, present in nonpregnant women as well. The role of long-standing sinusitis has been demonstrated by Sorri et al. As in pregnancy rhinitis, the only symptom of long-standing sinusitis may be nasal congestion. This reduction of other symptoms is possibly caused by a defect in the local immune response of the nose or sinuses or by reduced inflammatory cell function during pregnancy.
SUBJECTS AND METHODS

Twenty-seven nonsmoking healthy pregnant women aged 22 to 38 years (mean age, 28 years) without a history of either respiratory allergy or chronic nasal or sinus problems were included in the study. They had no nasal complaints upon entry. Nine of the women had no children previously, 13 women had 1 child each, and 1 woman had 3 children. All pregnancies were dated according to a routine ultrasound examination in gestational week 17.

The study plan is outlined below.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Gestational Week, Mean (Range)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>12 (7-15)</td>
</tr>
<tr>
<td>2</td>
<td>22 (20-23)</td>
</tr>
<tr>
<td>3</td>
<td>29 (27-30)</td>
</tr>
<tr>
<td>4</td>
<td>37 (35-38)</td>
</tr>
<tr>
<td>5</td>
<td>*</td>
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</tbody>
</table>

* Asterisk indicates that visit 5 was 1 month post partum.

Entry visit was planned as early in pregnancy as possible. After the initial visit, the participants noted morning levels of subjective nasal obstruction (0, no obstruction; 1, slight obstruction; 2, moderate obstruction; 3, severe obstruction; 4, total obstruction). They also measured nPEF as described earlier. After the nPEF, they performed ordinary oral PEF. For every occasion, the maximum value of the 3 recordings possible. We considered this important for inclusion of more “exact” methods, such as rhinomanometry, to make daily registrations possible. We also studied the relationship between objectively measured blockage and the different parameters during pregnancy, subtracted values between the visits were used, ie, values obtained at visit 2 were subtracted from values obtained at visit 1, and so forth. Spearman rank correlation was used.

All participants gave their informed consent. The study was approved by the Ethics Committee of Sahlgrenska University Hospital, Göteborg, Sweden.

Human growth hormone (hGH) is secreted in episodic bursts with low or indetectable levels between peaks. This pattern is replaced by a continuous secretion with rising values of a placental growth hormone variant (PGH) after the first trimester of pregnancy. This is when pregnancy rhinitis has been thought to occur. The PGH has an amino acid sequence that is different from that of hGH by 13 amino acid substitutions. The metabolic role of PGH is being investigated. As its secretion has been shown to be modulated by glucose, just like the secretion of hGH, a key function of protecting the fetus against a decrease of nutrient availability is suggested. In hGH treatment, effects similar to those induced by progesterone have been observed, eg, peripheral vascular dilatation and increased extracellular volume.

Peptide growth factors, especially insulinlike growth factor 1 (IGF-I) have been linked to regenerative activity in nasal mucosal cells. Furthermore, IGF-I has been proposed to be involved in the formation of nasal polyps. The IGF-I is associated with secretion of hGH and its level is also known to rise in the course of pregnancy, possibly caused by increased secretion of PGH.

The level of PGH was determined by an immunoradiometric assay performed with a specific monoclonal antibody against purified PGH and recombinant PGH as a standard as described earlier. The detection limit was 0.2 ng/mL. The intra-assay coefficient of variation was 3.3%, and the interassay coefficient of variation was 8.5%.

The hGH level was determined by immunoradiometric assay as described by the manufacturer (Biocode, Liège, Belgium).

STATISTICAL METHODS

When comparing the mean values of the different parameters for the group of women with pregnancy rhinitis and the group without rhinitis, values were transformed to logarithms when appropriate, and 2-way analysis of variance (ANOVA) for repeated measurements, followed by the Student-Newman-Keuls test, was used.

When analyzing the relationship between objectively registered blockage and the different parameters during pregnancy, subtracted values between the visits were used, ie, values obtained at visit 2 were subtracted from values obtained at visit 1, and so forth. Spearman rank correlation was used.

All participants gave their informed consent. The study was approved by the Ethics Committee of Sahlgrenska University Hospital, Göteborg, Sweden.
RESULTS

Four women did not complete the study; 3 women had miscarriages, and 1 woman left because of failing motivation. One woman without pregnancy rhinitis failed to complete visit 4 and, therefore, was excluded from the statistical evaluation. The remaining 22 women were included in the study. Except for 1 duplex pregnancy and 2 cesarean sections, 1 resulting from moderate eclampsia and 1 because of humanitarian indication, all pregnancies were completely normal. Gestational length at delivery varied between 37 and 42 weeks.

Five of the 22 women had pregnancy rhinitis, based on our criteria. When comparing the mean values for the different parameters of the 5 women with pregnancy rhinitis with the corresponding values for the remaining 17 women, there was a significant difference in 1 case only: PGH serum levels were higher in the group consisting of women with pregnancy rhinitis on all occasions throughout pregnancy ($P=.02$) (Figure 1). Thus, the mean values of serum levels of estradiol, progesterone, hGH, and IGF-I were similar in the 2 groups (Figure 2), as were the mean values of body weight (Figure 3).

All hormonal levels, as well as body weight levels, changed significantly with gestational length as expected in both groups (Figures 1-3).

The only significant correlation found between objectively registered blockage and the parameters listed above was regarding progesterone (Table). There was a strong correlation between visit 3 and visit 4 only ($r=0.63; P=.002$), whereas the other periods did not show any significant correlations.

COMMENT

This study demonstrates elevated serum levels of PGH in women with pregnancy rhinitis.

We have made a clinical definition of pregnancy rhinitis as “nasal congestion in the last 6 weeks or more of pregnancy without other signs of RTI and with no known allergic cause, disappearing completely within 2 weeks after delivery.” Five of the 22 women met these criteria. This group of women had significantly higher mean values of PGH at the 4 visits during pregnancy than the group of women lacking the diagnosis.
The International Consensus Report on the Diagnosis and Management of Rhinitis\textsuperscript{23} in 1994 proposed the existence of a hormonal rhinitis in acromegaly. The theory that hGH may induce changes in the mucosa of the upper airways is supported by Skinner and Richards.\textsuperscript{24} They reported a significantly increased frequency of mucosal hypertrophy and polyp formation in the sphenoid and ethmoid sinuses of patients with acromegaly, compared with patients with prolactin-producing adenoma. No such pathologic changes were found in the nasal mucosa, which, however, was examined after preoperative cocaine treatment. We believe that PGH may stimulate mucosal growth in a similar way and thereby induce pregnancy rhinitis.

We found no significant connection between pregnancy rhinitis and maternal body weight or the serum levels of estradiol, progesterone, hGH, or IGF-I. There was no conclusive correlation between objectively measured blockage and any of the parameters.

Although PGH levels were raised in pregnancy rhinitis, it did not correlate with changes in objectively registered blockage. This may be influenced by our very strict diagnostic criteria in contrast to the fewer registrations involved in the blockage evaluation. Furthermore, there is only a modest correlation between our objective and subjective data, as discussed earlier.

We have shown that raised serum levels of estradiol cannot possibly be a causative factor in nasal congestion of menstruation,\textsuperscript{21} and the present study confirms that this is true for pregnancy rhinitis as well. This is in conformity with our findings that objectively registered nasal blockage does not always increase during pregnancy. In fact, it may even decline, even though estradiol increases dramatically (unpublished data, 1997).

All the parameters changed in the course of pregnancy as expected, ie, estradiol, progesterone, PGH, IGF-I, and body weight levels rose progressively, whereas hGH levels decreased in all subjects. However, the pulsatile secretion of hGH and the decrease of its concentration during pregnancy makes the latter evaluation difficult.

The fact that objectively registered blockage correlated well with changes in progesterone during one period studied does not imply a causative relationship, but is interpreted as a coincidence, as the values during the other periods did not correlate well. Still, there is a possibility that progesterone plays a role in producing nasal congestion by local vascular pooling.\textsuperscript{7}

The mean weight loss after delivery was identical in the 2 groups. Thus, weight gain, representing retention of water, does not per se seem to induce nasal congestion, but there may still be a local retention, ie, edema in the mucosa. This may be a direct effect of the PGH on the nasal mucosa.

In summary, the present study shows that serum levels of PGH are elevated in pregnancy rhinitis, whereas serum levels of estradiol and progesterone are not. Water retention indicated by weight gain does not seem to be involved in the development of pregnancy rhinitis. What local nasal mechanisms are involved remains to be determined.

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REFERENCES

3. Toppozada H, Toppozada M, El-Ghazzawi I, Elwany S. The human respiratory...