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MAIN ARTICLE

Hormonal changes causing rhinitis in pregnancy among Malaysian women

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Abstract

Objectives: To investigate the aetiology of rhinitis occurring in pregnancy, by (1) describing the relationship between pregnancy rhinitis and serum oestrogen, progesterone, placental growth hormone and insulin-like growth factor, and (2) assessing the prevalence of pregnancy rhinitis among Malaysian women.

Methods: Prospective study involving 30 pregnant women followed at an ante-natal clinic for 14 months. Hormone levels were analysed during pregnancy and the post-partum period.

Results: Levels of all four hormones were elevated in the third trimester, compared with first trimester and post-partum values. Rhinitis patients had higher levels of oestrogen and insulin-like growth factor 1 in the third trimester than non-rhinitis patients, although these differences were not statistically significant. The prevalence of rhinitis was 53.3 per cent, with most cases occurring in the third trimester. Patients with pregnancy rhinitis had a higher prevalence of female babies, compared with non-rhinitis patients ($p = 0.003$).

Conclusions: Pregnancy rhinitis was significantly more common in women giving birth to female babies. Women with pregnancy rhinitis had a non-significant elevation in oestrogen and insulin-like growth factor 1 levels, compared with those without rhinitis.

Key words: Pregnancy; Rhinitis; Estrogen; Progesterone; Placental-Specific Growth Hormone, Human; Insulin Like Growth Factor 1

Introduction

Pregnancy rhinitis is defined as nasal congestion present during the final six (or more) weeks of pregnancy, without other signs of respiratory tract infection and with no known allergic cause, which disappears completely within two weeks of delivery.[1]

Nasal obstruction is a common complaint during pregnancy, and can be either physiological or pathological. Physiological obstruction occurs as a result of pregnancy-related hormonal and vascular changes.[1]

A previous study by Ellegard *et al.* (similar to the present one) noted that 22.7 per cent of pregnant women experienced pregnancy rhinitis, and attributed this to growth hormone ($p = 0.02$).[2] Human growth hormone is secreted in episodic bursts in the non-pregnant state. However, after the first trimester of pregnancy this pattern is replaced by continuous secretion, with rising values of a placental growth hormone variant. Ellegard and colleagues believed that this coincided with the onset of pregnancy rhinitis.

Serum progesterone levels are known to affect systemic blood volume. During pregnancy, rising levels of serum progesterone may induce nasal vascular smooth muscle relaxation, resulting in local vascular pooling.[2]

Different questionnaire-based studies have noted varying prevalences of pregnancy rhinitis: 11, 18.2, 26 and 32 per cent.[3–5]

Philpott *et al.* studied nasal physiological changes during pregnancy, using anterior rhinoscopy, peak inspiratory nasal flow, acoustic rhinometry, anterior rhinomanometry, mucociliary clearance time and rhinitis questionnaire response scores.[4] All tests showed a consistent decrease in nasal patency as gestation progressed, although only anterior rhinoscopy, anterior rhinomanometry, mucociliary clearance time and rhinitis questionnaire score results showed a statistically significant change.

An experimental study showed that exogenous oestrogen administration to male and female monkeys resulted in nasal mucosal swelling, with perivascular oedema.[6]

Insulin-like growth factor 1 has been linked to regenerative activity in the nasal mucosa and has also been implicated in the formation of nasal polyps, as shown in biopsy specimens of human nasal mucosa.[7,8]

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Objectives

The present study aimed (1) to describe any relationship between pregnancy rhinitis and serum levels of oestrogen, progesterone, growth hormone and insulin-like growth factor 1, and (2) to assess the prevalence of pregnancy rhinitis among Malaysian women.

Methods

This study was approved by the University Malaya Medical Centre Ethics Committee.

The study included 30 pregnant women attending the ante-natal clinic at the obstetrics and gynaecology department of the University of Malaya Medical Centre between June 2010 and August 2011. All patients gave their consent for inclusion in the study.

The study inclusion criteria were women aged 45 years or less who were in the first trimester of pregnancy, who had no previous history of nasal allergy or sinusitis prior to pregnancy, and who had a normal ear, nose and throat examination.

The exclusion criteria were known previous nasal symptoms, coexisting respiratory tract infection, asthma or sinusitis, growth hormone supplementation or growth hormone suppression treatment, and oestrogen therapy.

In their first trimester, patients were given a validated questionnaire to complete, followed by a nasal examination via anterior rhinoscopy to exclude nasal pathology.[9] Blood samples were drawn for the assessment of oestrogen, progesterone, growth hormone and insulin-like growth factor 1 levels.

The same patients were followed up in their second and third trimesters, and post-partum. During these follow-up appointments, blood samples were drawn and nasal examination repeated. Each patient's hormonal changes were correlated with her nasal symptoms.

Statistical analysis was performed using SPSS version 13 software. Categorical data analysis was performed using the chi-square test, and continuous data analysis was performed by the analysis of variance test. A p value of less than 0.05 was considered statistically significant.

Hormone results were compared with normal antenatal and post-partum values obtained from three different studies.[10–12]

TABLE I
MEAN HORMONE LEVELS IN NORMAL PREGNANT POPULATION

Hormone	Trimester			Post-partum
	1st	2nd	3rd	
Oestrogen	4.38	4.7	12	0.03
Progesterone	29.9	65.5	118	0.61
GH	1.65	4.09	9.57	1.46
IGF	159.6	164	331	153.7

Data represent serum concentrations in ng/ml. GH = growth hormone; IGF = insulin-like growth factor

Results

Fifty-six patients in the first trimester of pregnancy were recruited into the study. Of these 56 patients, only 30 completed the study. Of the 26 patients lost to follow up, 16 defaulted after their second trimester, 5 aborted, and 5 departed for their home town at the beginning of their third trimester, for their delivery. The mean age of the remaining 30 patients was 31 years.

Of the 30 patients who completed the study, 16 had rhinitis during their pregnancy.

Figures 1 to 4 compare the results of hormone analysis for the rhinitis and non-rhinitis patients. Patients suffering rhinitis had raised levels of oestrogen and insulin-like growth factor 1 during pregnancy, compared with non-rhinitis patients, although these differences were not statistically significant.

There was no significant difference in mean oestrogen levels during the third trimester, comparing the rhinitis and non-rhinitis groups ($p = 0.335$) (Figure 1).

Likewise, the raised level of insulin-like growth factor 1 seen in the rhinitis patients during the third trimester, compared with non-rhinitis patients, was also not statistically significant ($p = 0.329$) (Figure 2).

There was no significant difference in mean growth hormone levels in the third trimester, comparing the rhinitis and non-rhinitis groups ($p = 0.850$) (Figure 3).

Progesterone levels in the rhinitis group showed only a slight elevation in the second trimester, compared with the non-rhinitis group, and were actually lower during the third trimester. This pattern does not correlate with patients' complaints of suffering rhinitis only during the third trimester. There was no significant difference in mean progesterone levels in the third

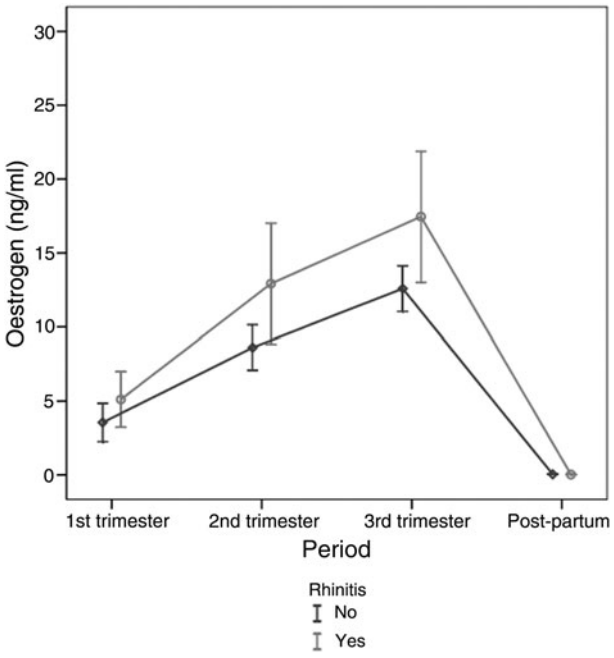


FIG. 1
Mean oestrogen levels in rhinitis and non-rhinitis groups.

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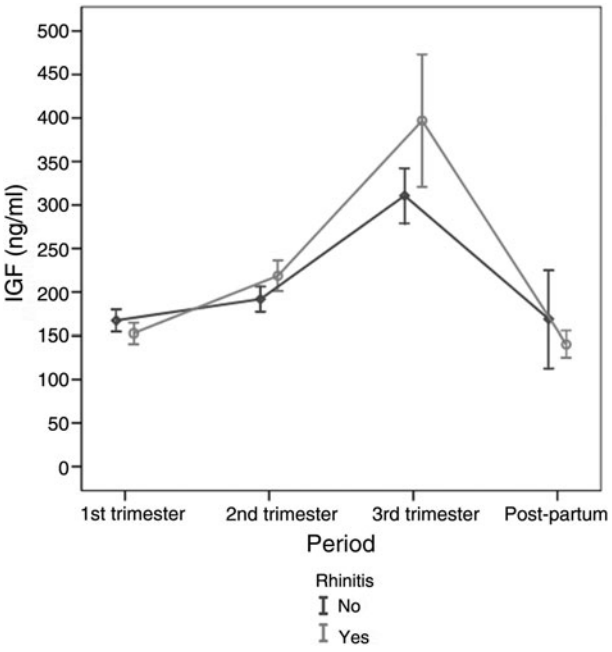


FIG. 2
Mean insulin-like growth factor 1 (IGF) levels in rhinitis and non-rhinitis groups.

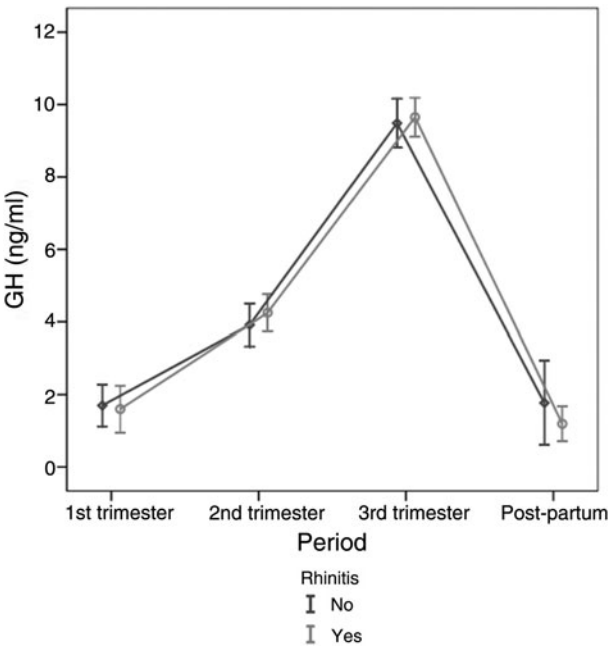


FIG. 3
Mean growth hormone (GH) levels in rhinitis and non-rhinitis groups.

trimester, comparing the two groups ($p = 0.803$) (Figure 4).

Tables II and III compare levels of the four hormones in patients with and without rhinitis, respectively.

We also analysed the sex of the baby born, to investigate whether this had any association with the prevalence of maternal rhinitis. Interestingly, of the 16 patients with pregnancy rhinitis, 14 (87.5 per cent) had female babies, compared with 7 of the 14 (50 per cent) non-rhinitis patients; this difference was statistically significant ($p = 0.003$).

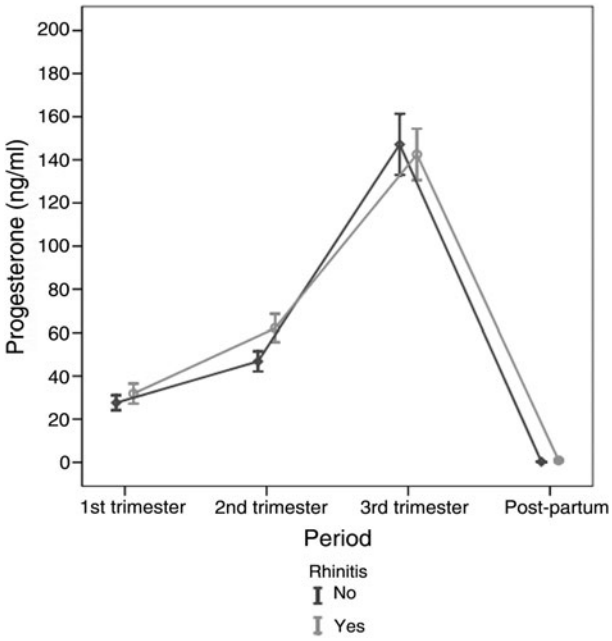


FIG. 4
Mean progesterone levels in rhinitis and non-rhinitis groups.

TABLE II
MEAN HORMONE LEVELS: RHINITIS GROUP*

Hormone	Trimester			Post-partum
	1st	2nd	3rd	
Oestrogen	5.11	12.91	17.45	0.02
Progesterone	31.88	62.13	142.50	0.89
GH	1.60	4.25	9.65	1.19
IGF	152.81	218.69	397.00	140.38

*$n = 16$. Data represent serum concentrations in ng/ml. GH = growth hormone; IGF = insulin-like growth factor

TABLE III
MEAN HORMONE LEVELS: NON-RHINITIS GROUP*

Hormone	Trimester			Post-partum
	1st	2nd	3rd	
Oestrogen	3.55	8.61	12.58	0.04
Progesterone	27.64	46.79	147.14	0.29
GH	1.70	3.91	9.49	1.77
IGF	167.36	191.79	310.71	168.93

*$n = 14$. Data represent serum concentrations in ng/ml. GH = growth hormone; IGF = insulin-like growth factor

Discussion

Nasal obstruction is a common complaint during pregnancy. It can be divided into physiological and pathological types. Physiological obstruction occurs as a

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result of hormonal and vascular changes during pregnancy, similar to those changes occurring during menstruation and menopause.[1]

Pregnancy rhinitis is defined as nasal congestion present during the last six or more weeks of pregnancy, without any other signs of respiratory tract infection and with no known allergic cause, which disappears completely within two weeks of delivery.[13]

Pregnancy involves a series of complex physiological changes. The pregnant woman's fluid status undergoes changes which alter the physiology of the nasal passage. The plasma volume of a pregnant woman increases progressively throughout pregnancy, commencing in the sixth to eighth week and peaking at 32 weeks, at a volume of 4700 to 5200 ml, representing a 45 per cent increase above non-pregnant levels. This expansion is thought to occur due to increased oestrogen secretion stimulating the renin angiotensin aldosterone system, which in turn stimulates water and sodium retention. This water retention results in oedema of the nasal mucous membrane, resulting in nasal obstruction.[1,14]

Secretion of oestrogen and progesterone by the corpus luteum is believed to contribute to nasal blockage during early pregnancy. By the third month of the pregnancy, secretion of these hormones is taken over by the placenta.[1] Pregnancy rhinitis is thought to be due to the circulating steroid sex hormones.[1]

Progesterone thickens the endometrium and plays a major role in maintaining pregnancy. Withdrawal of progesterone at term induces labour. It has been proposed that progesterone is responsible for pregnancy-induced nasal congestion via the twin effects of increased blood volume and enhanced vasodilation.[2]

After the 12th week of pregnancy, secretion of growth hormone increases. In the first trimester, human growth hormone is secreted in episodic bursts. After the first trimester, this is replaced by continuous secretion of placental growth hormone, leading to increasing levels.[13] This hormonal environment is essential for the growth of the fetus.

Growth hormone exerts its major effect of increased cell growth via stimulation of insulin-like growth factor 1. Levels of this latter hormone are also known to rise during the course of pregnancy. Insulin-like growth factor 1 has been linked to the regenerative activity of the nasal mucosa and also to the formation of nasal polyps. Hansson *et al.* have shown that the presence of peptide growth factors within the human nasal mucosa could correlate with its maintenance and repair.[7] In their study, immunohistochemical investigation of biopsy specimens of healthy human nasal mucosa (from subjects aged 6 to 72 years) showed that intense concentrations of insulin-like growth factor 1 were demonstrable in areas with deficient epithelial lining and inflammatory cells. Variable insulin-like growth factor I immunoreactivity was found in vascular wall cells, fibroblasts, macrophages and exocrine gland cells in the reactive nasal mucosa.

In the nineteenth century, theories relating nasal obstruction to female sex hormones were proposed. In 1881, a case report described a woman with ozena (atrophic rhinitis) which worsened during menstruation. In 1884, MacKenzie quoted Ayurvedic medical practices, together with Hippocrates and Celcus, in a discussion of his own and other nineteenth century writers' observations on the erection of the nasal turbinate structures during menstruation and sexual excitement. In 1898, he expounded his theory of nasal congestion. In 1892, Endriss described epistaxis occurring during menstruation.[14]

Experimental studies in 1936 noted that oral or intramuscular administration of oestrogen to monkeys resulted in marked swelling of the nasal mucosa, with perivascular oedema.[6]

A 2006 study of 20 cases of pregnancy-related vasomotor rhinitis reported that nasal symptoms commenced during the third to the seventh month of pregnancy, and thereafter persisted until term. The study concluded that such rhinitis was related to oestrogen, and also proposed that the excess growth hormone levels occurring during pregnancy predisposed the nasal structures to vasomotor rhinitis in some way.[14]

The occurrence of nasal hyperaemia with oedema and hyper-secretion during menstruation has also been demonstrated. The influence of psychological factors on the causation of such symptoms during menstruation and pregnancy has been emphasised.[14]

Biochemical studies of biopsy mucosa from pregnant women with and without nasal symptoms have been performed.[3] Mucosa from women with nasal symptoms was found to have increased cholinergic activity in the nasal blood vessels and surrounding mucosal glands; no such changes were found in women without nasal symptoms. It was concluded that oestrogen influences the nasal mucosa via a direct cholinergic effect, increasing local production of acetylcholine. Another study reported that 32 per cent of 79 women questioned at the end of their pregnancy described having frequent nasal 'stuffiness' throughout the pregnancy.[4]

Philpott *et al.* have suggested that progesterone may have an influence on fibroblasts present in the nasal mucosa of pregnant women, which may subsequently affect the extracellular matrix.[4] These authors have also proposed that oestrogen and progesterone alter the concentration of the neurotransmitter substance P, resulting in nasal congestion. Philpott and colleagues evaluated multiple nasal airway parameters in 18 pregnant women. Assessment included anterior rhinoscopy, peak inspiratory nasal flow, acoustic rhinometry, anterior rhinomanometry and questionnaire completion, undertaken from the first to the third trimester and also during the post-partum period. A trend was identified consistent with decreasing nasal patency. This information confirms the effect of pregnancy on the nasal mucosa, which coincides with an increase

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in female sex hormone levels with gestational age and a return to normal levels post-partum.

Incaudo and Takach measured the nasal patency of 40 pregnant women, using Gertner's plate method, in all three trimesters and also within three months of delivery. Nasal patency was found to increase significantly as pregnancy progressed ($p < 0.001$). Study findings confirmed that rhinological changes coincided with rising gestational age, and reverted to normal post-partum.[15]

Ellegard *et al.* conducted a study similar to our own, comparing levels of oestrogen, progesterone, growth hormone and insulin-like growth factor 1 in pregnant women and assessing the influence of these hormones on pregnancy rhinitis.[2] This study identified pregnancy rhinitis in 5 out of 27 (22.7 per cent) patients. These five patients showed an increase in growth hormone levels which was not related to weight gain.

In our study, we analysed 30 pregnant women selected from a population of women attending the ante-natal clinics of University Malaya, Malaysia. The prevalence of pregnancy rhinitis was 53.3 per cent. Of the 4 hormones analysed, raised levels of oestrogen (Figure 1) and insulin-like growth factor 1 (Figure 2) were found in 16 patients, although this elevation was not statistically significant. No significant change was noted for growth hormone or progesterone (Figures 3 and 4).

Our study also recorded the sex of the babies born to our 30 patients. Female babies were more common among patients with pregnancy rhinitis: 14 of the 16 rhinitis group patients had female babies, compared with 7 of the 14 non-rhinitis group patients ($p = 0.003$). It is possible that the female sex hormones produced by female fetuses act as an additional factor causing rhinitis in their mothers.[16]

- **This study assessed oestrogen, progesterone, growth hormone and insulin-like growth factor 1 in pregnant Malaysian women with and without rhinitis**
- **Rhinitis occurred in 53.3 per cent of women**
- **There was a trend towards raised oestrogen and insulin-like growth factor 1 in the rhinitis group**
- **Significantly more rhinitis patients had female babies**

Insulin-like growth factor 1 exerts its action via stimulation of growth hormone. In our study group, insulin-like growth factor 1 levels were elevated but there was no significant rise in growth hormone levels; in contrast, Ellegard et al. did find an increase in growth hormone levels.[2]

A direct effect of insulin-like growth factor 1 has been demonstrated in the causation of nasal polyps.[7,17] However, nasal examination of our patients with pregnancy rhinitis revealed no nasal polyp formation.

Our study was limited by its small sample size. In addition, taking into consideration the duration of pregnancy would have enabled the calculation of more accurate results.

Conclusion

In this population of pregnant Malaysian women, pregnancy rhinitis was observed in 53.3 per cent. In afflicted patients, rhinitis occurred in the last trimester and disappeared within a month of delivery.

Patients with pregnancy rhinitis had raised levels of oestrogen and insulin-like growth factor 1, although these differences were not statistically significant.

In additional, female babies were more common among the rhinitis patients (87.5 per cent), compared with the non-rhinitis patients (50 per cent) ($p = 0.003$).

Pregnancy rhinitis is a common cause of discomfort which can reduce patients' quality of life. Further research is needed to investigate safe methods of relieving nasal congestion in pregnant women.

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