Pregnancy-induced rhinitis*

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Summary

Background: Pregnancy-induced rhinitis (PIR) is often misclassified and under-diagnosed. There is currently no cure or optimum symptomatic treatment.

Objective: To summarize current knowledge of PIR and assess evidence supporting treatment options.

Type of review: Structured literature search.

Search strategy and evaluation method: Review of English-language articles addressing evidence for aetiology, classification, differential diagnosis or treatment options for PIR. Comparisons to management of other types of rhinitis in pregnancy are also considered.

Results: Incidence and prevalence of PIR vary widely between studies. Hormonal changes have a presumed aetiological role, although present evidence is scanty. Smoking appears to be the only agreed identifiable risk factor. Distinction between PIR and other types of rhinitis in pregnancy, especially allergic rhinitis, is important as effective treatments differ. Management of PIR focuses on minimal intervention required for symptom relief.

Conclusions: Although PIR is temporary, its impact on patients' quality of life can be profound. Advice and conservative treatment provide the mainstay of clinical management. None of the currently available medical options offer an ideal solution. Any potential benefit gained should be balanced against risks to the foetus. Clarifying the definition of this separate category of rhinitis will lead to better recognition, with prompt and appropriate treatment.

Key words: rhinitis, pregnancy induced, smoking, IgE, pyogenic granuloma

Introduction

The potential connection between nasal symptoms and the female hormonal cycle was noted as early as the late 18th century [1]. Observations of a cyclical change in symptoms related to the menstrual cycle were expanded to include the changes seen during pregnancy. In 1943, a case series of 'vasomotor rhinitis' was presented, where all bar one resolved post partum [2].

A distinction must be drawn between non-specific "rhinitis during pregnancy" and true pregnancy-induced rhinitis. Rhinitis during pregnancy includes all causes of rhinitis such as allergic [3,4], vasomotor rhinitis and rhinitis medicamentosa, which are present before, during and after pregnancy. In a study of 328 atopic asthmatics, 34% noted worsening of their nasal symptoms during their pregnancy, 15% plateaued and 45% improved [5]. Pregnancy-induced rhinitis (PIR), however, is a different clinical entity. It may manifest at any point during pregnancy. PIR can be defined clinically as 'nasal congestion that is not present prior to pregnancy, typically manifests itself in the second or third trimester, lasts 6 or more weeks with no known allergic cause, and resolves completely within 2 weeks post delivery [6]. PIR may be misclassified when an allergic component is also present [7].

Methods

An online structured literature search (Medline (1950-), Embase (1980-), Pubmed (1950-), using the search terms "pregnancy AND rhinitis", was conducted. We reviewed all 60 relevant English-language articles and all related cited literature, which addressed the evidence for aetiology, classification, differential diagnosis and treatment options available for PIR. Management options for other types of rhinitis in pregnancy were considered for comparison.

Incidence and prevalence

Estimates for the incidence of PIR vary, often including all forms of rhinitis during pregnancy. Studies with relatively small numbers indicate prevalence of 18% [8] to 30% [9] for rhinitis in pregnant women. Shushan et al. used questionnaires and anterior rhinoscopy in 109 primigravidas and found the incidence of PIR to be 9% [10]. The largest population based multicentre cross-sectional questionnaire survey study using 599 participants (excluding all those who have suffered from nasal complaints prior to pregnancy) determined the incidence of PIR to be 22% [11]. When assessing the symptom of 'nasal stuffiness' , one Swedish study found prevalence of 42% in the 36th week of pregnancy with 11% of women complaining of congestion throughout the duration of the study [12]. This wide variation of incidence and prevalence rates demonstrates the difficulty in assessing the true figure of PIR and the importance of defining this disease entity correctly.

Clinical features

Common with other nasal conditions such as rhinosinusitis, allergic/ non-allergic rhinitis and nasal polyposis, nasal congestion is the primary nasal symptom in pregnancy induced rhinitis. In general, nasal congestion is due to a combination of factors: increased vascular pooling of blood, decrease in vasomotor tone, and oedema from plasma leakage into the nasal stroma [13,14]. Whilst no established histopathological evidence is available for the above factors in pregnancy induced rhinitis (as it would require nasal biopsies from pregnant women), it is appropriate to assume that similar physiological end-processes are involved. PIR may be indistinguishable from other possible differential diagnoses until relief from symptoms post-partum. Nasal pyogenic granuloma gravidarum is a different clinical entity from PIR. It most often presents as a unilateral vascular polypoid lesion in the nasal cavity, often arising from the septum although it can occasionally be found on the hard palate, tongue and gingivae. Characteristically bony destruction or invasion is absent [15].
The natural history is involution following delivery. Repeated epistaxis may require cautery with only occasional need for microembolisation or surgical resection [16]. The need for surgical management is rare but has been reported on a handful of occasions [17].

Possible aetiology

Present understanding of the physiological mechanisms behind PIR is lacking. Although many possible aetiological factors have been proposed, at the present time no single viable pathophysiological explanation is available to clearly explain the changes seen in pregnancy. We outline some possible factors below, and provide the available evidence.

Sex hormones

The role of sex hormones is much debated in PIR. Early electromicroscopy studies of nasal mucosae during pregnancy and the menstrual cycle show increased glandular and phagocytic activity and increased mucopolysachharides [18,19]. There is some evidence that nasal physiology does alter with the menstrual cycle. Nasal mucociliary clearance [20] is decreased, anterior rhinomanometry shows increased resistance [21] and peak inspiratory flow rate is decreased around the peri-ovulatory period. Conversely, congestion was found to be worse during menses (i.e. when oestrogen levels are lowest) [22].
Physiological studies demonstrate significant alterations in anterior rhinoscopy, anterior rhinomanometry and rhinitis questionnaire scores consistent with decreasing nasal patency with pregnancy progression [23]. Oestrogen has been suggested as the possible cause of these changes possibly via increased histamine receptor expression on microvascular and epithelial cells [24].
Circulating blood volume increases in pregnancy and progesterone may compound this effect by enhancing vasodilatation [25]. Although fibroblasts with progesterone receptors are found in the extracellular matrix [26], immunostaining of endothelial cells conversely demonstrates marked activity for oestrogen receptors and not progesterone receptors [27]. Clear evidence for the role of progesterone in PIR is still lacking.
Clinical evidence is also conflicting. If increased oestrogen levels do cause increased nasal congestion, all women should have worsening or increasing symptoms around the pre-ovulatory phase of the menstrual cycle, and all pregnant women should experience deterioration in their symptoms with the progression of their pregnancy. In addition, oestradiol and progesterone levels are not elevated when comparing PIR symptomatic versus. asymptomatic pregnancies [28]. Furthermore, the number and intensity of oestrogen receptors demonstrated by positive immunostaining shows no difference between pregnant women, non-pregnant women and men [27].

Neuropeptides

Serum levels of vasoactive intestinal polypeptide, a potent vasodilator, do not support its possible role in inducing rhinitis via vasodilatation [29]. However, a small study in postmenopausal women assessed the possible effects of HRT in provoking nasal congestion [30]. It suggests the action of oestrogen on the nasal

Table 1. Differential Diagnosis of Rhinitis in Pregnancy

Condition	Suggestive features	Notes
Rhinitis Medicamentosa*	Long term use of topical decongestant	Can take longer to resolve than in non-pregnant women
Sinusitis*	Unilateral pain, and purulent nasal discharge, though nasal congestion may be the only symptom [97] present in pregnancy.	Diagnosis may be more apparent on anterior rhinoscopy
Nasal granuloma gravidarum (Histologically similar to pyogenic granuloma)	Epistaxis is a common feature Unilateral mass in the nasal vault	Bony destruction or invasion is absent. Usually involutes following delivery The need for surgical resection is rare.
Allergic rhinitis	Can test for specific IgE in vitro	Especially airborne allergy e.g. house dust mite.
Upper respiratory tract infection	Not as long-lived and not confined to nose	

* Can be both a differential diagnosis and complication of PIR.

mucosa is mediated by increased gland secretion, vasodilatation by VIP and Substance P, as well as decreased neuropeptide Y-mediated vasoconstriction.

Growth hormones

Placental growth hormone has been found to be present in significantly higher concentrations [28] in PIR symptomatic pregnancies. During pregnancy the normal pulsatile secretion and release of human growth hormone is replaced by continuous and increasing production of placental growth hormone. Acromegalic patients do have an increased frequency of nasal polyposis and nasal mucosal hypertrophy [31] whereas prolactinoma patients do not.

Normally, pituitary prolactin secretion is inhibited by dopamine. Although prolactin increases during pregnancy, it is unlikely to contribute to PIR as quinagolide, which is a dopamine agonist, and hence inhibits prolactin secretion, can cause nasal congestion as a side effect.

Risk factors

To date, smoking is the only significant risk factor that has been shown to increase the risk of PIR [32]. In the same study, specific IgE to house dust mite was also a significant predisposing factor to the development of symptoms. Pre-existing asthma, hay-fever and the month of conception did not influence the development of gravidarum rhinitic symptoms [11]. Maternal age, parity and sex of the child seem to have no influence over the development of PIR [12,32]. No association has been demonstrated between PIR and hay-fever or asthma. Furthermore, there is no increase in nasal hyperactivity in PIR as is the case in allergic rhinitis associated with asthma [33].

Given that nasal mucosa electron microscopy of allergic rhinitics yields an identical picture to that seen in PIR [18], and the fact that a significant proportion of PIR patients show significant in vitro reactions to house dust mite antigen, it has been suggested that PIR patients represent a subset of subclinical allergic rhinitis. However, these patients will recover from their symptoms spontaneously after delivery, (by definition of true pregnancy induced rhinitis) and serum markers for allergic disease (such as soluble intercellular adhesion molecule-1 (sICAM-1) are not elevated in PIR [32].

Discussion

Clinical significance of PIR

PIR induced nasal congestion can adversely affect maternal sleep [34,35]. If severe, it may be associated with snoring or obstructive sleep apnoea (OSA) [36] although the latter may be due to a combination of other factors such as weight gain. OSA is thought to be a significant contributor in the development of maternal hypertension, preeclampsia and intrauterine growth retardation [37,38].

Mouth breathing as a consequence of PIR interferes with nitric oxide (NO) transmission from nasal airway to lungs, along with preventing the filtering, warming and humidification of inhaled air [39] altering normal nasal physiology. Unremitting nasal obstruction seen in PIR can potentially lead to self-administration of topical decongestants [40] and a subsequent development of rhinitis medicamentosa which does not resolve on delivery [41].

There is no evidence to date to link maternal rhinitis with a less favourable pregnancy outcome. Savilahti et al. have postulated that maternal atopy, favouring a Th2 skewed immune picture and therefore maternal rhinitis itself favours a better fetal outcome as their study demonstrated an association between maternal allergic rhinitis and higher birth weights [42]. These findings may be confounded by higher incidence of atopy in higher socioeconomic groups who have better nutrition and

tend to smoke less.

Treatment of PIR

Identifying the correct cause of rhinitis in pregnancy is paramount, as the treatment of PIR differs from that of allergic rhinitis in pregnancy.

General advice and conservative management options

True pregnancy induced rhinitis will abate post partum, so patient education should form a vital part of a holistic approach to treatment [43]. Providing information on PIR to pregnant women will help women cope with symptoms should they go on to develop the condition. They are then less likely to resort to topical sympathomimetics and should avoid developing rhinitis medicamentosa [44]. Exercise can help patients, by reducing nasal decongestion [45], controlling weight gain, and enabling a better sleep pattern through normal post-exercise fatigue. Raising the head of the bed to an angle of 30-45 degrees will also help with nocturnal nasal congestion [46]. Nasal saline douches may provide good symptomatic relief in PIR [47]. Although no studies on its use specifically in PIR exist, summary documents as per EPOS 2012 outline its beneficial use in chronic rhinosinusitis without nasal polyps [48] so evidence for their use in PIR is level IV at best. Finally, a variety of different mechanical devices exist for dilating the nasal valve, and have been shown to subjectively improve nasal breathing in pregnancy [49-51].

Medical therapy

Treatment of PIR must balance the expected benefit to the mother with the potential risk to the developing foetus. Patient perception of increased risk of congenital malformation [52] and first trimester drug use differ from evidence suggesting that such increase may not exist [53]. Older drugs with an established safety profile are preferable to newer agents, and the lowest therapeutic dose should be used [54,55]. Non-medicinal interventions such as nasal saline washes and external nasal dilator strips may provide symptomatic relief [49]. Allergen avoidance in cases of allergic rhinitis during pregnancy is important [56]. It is not clear whether allergen avoidance improves symptoms in house dust mite atopic PIR patients. Albeit high house dust mite specific IgE levels predispose to pregnancy rhinitis [32], starting immunotherapy in pregnancy is not recommended [57]. Likewise, allergen dosage should not be increased, however maintenance of immunotherapy at a stable dose was shown to be safe in two separate studies with 10,958 and 12,159 women.

Intranasal therapy

Topical treatments which have a good safety profile can be used to minimize the impact of PIR symptoms on the quality of life of the mother [60]. Decongestants give good temporary relief from nasal obstruction, but the necessity of extended use throughout pregnancy, makes the development of rhinitis medicamentosa very likely [61]. This will not resolve spontaneously on delivery [62], even if only used in the evenings [63].

Data on topical corticosteroid use in pregnancy is limited. They are effective in a wide range of rhinitic conditions, although fluticasone was not found to be particularly helpful for pregnancy induced rhinitis [64]. They can be useful in treating coexistent rhinitis medicamentosa [65], but do not provide immediate symptomatic improvement. In terms of safety, studies from inhaled steroid treatment for asthma in early pregnancy are reassuring [66]. Topical nasal corticosteroids have been shown to have no adverse effect on pregnancy progression in 53 women treated for 8 weeks in a placebo-controlled, randomized, double-blind study [64]. A case control study looking at drug use associated cardiac defects suggests a weak association between intranasal but not inhaled budesonide and less severe general cardiac defects [67]. A historical study of turbinate injection of corticosteroids in 21 pregnant participants demonstrated no adverse effects but within the context of limited follow-up [68].
Use of topical decongestant in the form of phenylpropanolamine (PPA) results in no improvement on nasal congestion after 7 days [69]. Table 2 summarises drug studies in pregnancy rhinitis.

Implications for PIR treatment from treating pregnant asthmatics

Data from pregnant asthmatics demonstrate no correlation between major congenital malformations [70], intra-uterine growth retardation [71] and common allergy/ asthma drug use, including inhaled corticosteroids. Similarly, a three year population based study (1995-1998) on all Swedish children showed no correlation between adverse pregnancy outcome and inhaled budesonide use [72]. Narrowing patient selection to moderate/ severe asthma and asthma exacerbations had a significant effect on pregnancy outcome as demonstrated by low birth weight, preterm delivery and small for gestational age newborns [73]. Present guidelines from the British National Formulary advocate optimal asthma control with adequate medical therapy to prevent exacerbations and worsening of overall asthma severity.

Mechanical therapy

Nasal continuous positive airway pressure (CPAP) is an appropriate option in cases of OSA secondary to PIR [74]. Maternal OSA has consequences for the fetal outcome including lower mean Apgar scores and birth weights [75]. Nasal CPAP is effective in reducing maternal nocturnal hypertension, which is associated with an increased risk of developing preeclampsia [76]. The CPAP pressure may need readjustment over the course of the pregnancy [77]. Spring loaded external nasal dilators were shown to be efficacious in a small study of 24 patients [51].

Surgery

As PIR will spontaneously resolve on delivery, surgical methods

Table 2. Summary of drug studies treating rhinitis in pregnancy.

Author	Drug	No. of Patients	Dose/ Duration	Outcomes	Side Effects	Level of evidence
Ellegard [64]	Fluticasone	53 (27 placebo / 26 active)	100 µg each side bd topical	No change: symptom scores / rhinoscopy / rhinometry	No change: maternal cortisol, fetal growth, pregnancy out-come	Ib (DBRPC)
Toll [69]	Phenylpro-panolamine	38 (18 placebo / 20 active)	50 mg bd for 1/52 topical	No change: symptom scores, rhinostereo-metry	No change: blood pressure	Ib (DBRPC)
Turnbull [51]	Nasal Dilator	24 (12 placebo / 12 active)	Spring loaded	Significantly better in treatment group. 3 day baseline and 3 day treatment period: Quality of sleep / breathing	No side effects	Ib (DBRPC)

should only be considered in very severe cases, such as the failure of CPAP in a woman with OSA due to PIR [78]. In rare cases where surgery is indicated, non-invasive methods for inferior turbinate reduction that do not require a general anaesthetic, such as surface electrocautery, laser, radiofrequency ablation or cryotherapy, or the use of mandibular advancement devices [79] are preferable. The degree of symptomatic relief afforded by these treatments, as well as the side effects, are largely unpredictable and may vary between patients [80].

We have summarised the above treatment options and propose a treatment ladder balancing benefits with risk for both mother and unborn child (Figure 1).

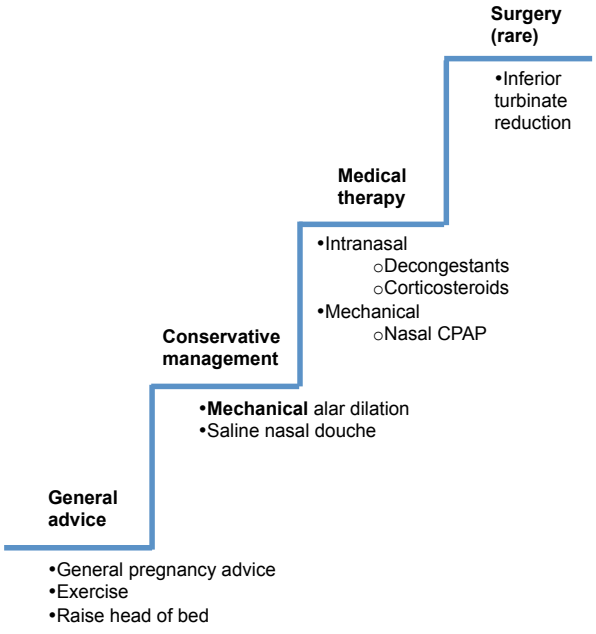

Figure 1. Proposed management ladder for pregnancy induced rhinitis.

Oral therapy Controversies

Systemic corticosteroid use

No rigorous safety studies exist for the use of oral steroids in pregnancy, and at present there is no good clinical data to advocate their use. Short courses of systemic steroids may have a place in weaning patients off nasal decongestants [8], but prolonged or repeated use should be avoided to prevent adrenal suppression, low birth weight and congenital malformations especially cleft lip [81].

Oral decongestant teratogenicity

Links have been proposed between oral decongestant use in the first trimester and development of VSD [82], and specifically between the use of pseudoephedrine and gastroschesis and small intestine atresia [83]. However, no adverse outcomes were seen with pseudoephedrine in an earlier case control study of

Table 3. FDA pregnancy risk categories.

A	Controlled human studies have demonstrated no fetal risk
B	Animal studies have demonstrated no fetal risk but no human studies OR animal studies have demonstrated adverse effects, but controlled human studies have shown no fetal risk
C	No adequate human or animal studies OR adverse effects on animal studies but no adequate human studies
D	Evidence of fetal risk in human studies, but benefits may outweigh risks
X	Evidence of fetal risk in human studies, risks outweigh any benefit

Table 4. FDA Risk rating of drugs used to treat rhinitis in pregnancy.

Drug	Category
Intranasal corticosteroids	
Budesonide	B
Beclomethasone	C
Fluticasone	C
Triamcinolone	C
Flunisolide	C
Chromolyn	B
Antihistamines	
Fexofenadine	C
Desloratidine	C
Loratidine	B
Cetirizine	B
Chlorpheniramine	B
Diphenhydramine	B
Clemastine	B
Tripelenamine	B
Hydroxyzine	C
Decongestants	
Pseudoephedrine	C
Antishistamine/ Decongestant	
Loratidine/ pseudoephedrine	B
Fexofenadine/ pseudoephedrine	C
Cetirizine/ pseudoephedrine	C
Other nasal sprays	
Azelastine	C
Ipratropium bromide	B
Oxymetazoline	C

2,509 pregnant women [84,85], and the main constituent of most topical nasal decongestants, ephedrine and pseudoephedrine, are not proven to have teratogenic effects [86]. Although systemic decongestants lack the rebound effect of topical preparations, their systemic side effects can include tachycardia, anxiety and insomnia.

Antibiotics

Antibiotics have no place in treating pure PIR (they are however required for sinusitis in pregnancy at elevated doses due to increased renal clearance in pregnancy) [87].

Overlap in management strategies with allergic rhinitis

In allergic rhinitis, allergen avoidance and the use of non-medicinal treatment such as saline nasal douches, should be considered alongside topical steroids with or without the addition of chromoglycate [88]. Concomitant asthma will also improve with adequate treatment of allergic rhinitis during pregnancy [89].
A number of prospective controlled cohort studies to date have demonstrated no teratogenic or embryotoxic effects [90,91] with oral antihistamines [92]. Anti-histamine usage in pregnancy is probably best limited to the purely allergic group, with topical treatment preferred over systemic administration. Topical treatments may alleviate rhinorrhoea and sneezing but their effect on nasal congestion is limited. A meta-analysis has demonstrated no increase in fetal malformations with first trimester first generation antihistamine use [93]. However, second-generation oral antihistamines have the benefit of less sedating and anticholinergic side effects, and are also considered safe [94].

Evidence on the use of sodium chromoglycate in pregnancy suggests no association between its use and teratogenicity [95]. In addition, it has a long, well established clinical history and an excellent safety profile. It can offer good symptomatic relief from nasal itching and sneezing in allergic rhinitis during pregnancy and can be used as first line treatment [96]. Finally, the use of the anti-muscarinic agent, ipratropium bromide is not known to be associated with teratogenicity and may be an appropriate option if marked rhinorrhoea is a feature during the second and third trimester of pregnancy although no studies on its use in PIR exist.

Conclusion

The impact of PIR on patients' quality of life can occasionally be profound, but the potential benefit to be gained from any treatment must always be balanced against the risks to the foetus. Clear and appropriate diagnosis of PIR is the first step in ensuring adequate and suitable management. General advice, patient education and conservative treatment should provide the mainstay of clinical management. Topical steroids are unlikely to provide appreciable benefit. Use of topical nasal de-

congestants should be avoided but may be necessary for short-term relief of severe symptoms. Prudent management aims to minimise exposure to medication whilst maintaining maximum symptomatic relief.

Key Points Summary

- Pregnancy-induced rhinitis is a separate entity from allergic rhinitis in pregnancy, and as such may not respond to allergic rhinitis treatment.
- Smoking and IgE to house dust mite are the only identifiable risk factors for developing pregnancy induced rhinitis
- Patient education of the remitting nature of PIR forms the cornerstone of management. A cautious stepwise approach to medical management should be adopted, to minimise the chances of risk to the foetus.

Author contribution

NO takes responsibility for the integrity of the content of the paper and is the principal author. EM provided second authorship providing help with literature search, paper selection and summary writing. NB was senior reviewer.

Conflict of interest

None declared.

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