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Otolaryngology -- Head and Neck Surgery 2013 148: 717 originally published online 20 February 2013
DOI: 10.1177/0194599813477837

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What is This?
The Rhinological Manifestations of Women’s Health

Alexander J. Saxby, MBChB, FRACS1, Pia Pace-Asciak, MD, MASc1, Rachelle C. Dar Santos1, Neil K. Chadha, MBChB, FRCS1, and Frederick K. Kozak, MD, FRCSC1

No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. To systematically review the literature and appraise the evidence reporting the effects of women’s health, including pregnancy, postpartum, menstruation, oral contraception, menopause, and hormone replacement therapy, on common rhinological pathologies and nasal physiology.


Review Methods. Title review, abstract screening, and then full paper analysis were undertaken by 2 authors independently. Level of evidence was graded according to the Oxford Centre of Evidence Based Medicine 2011 criteria and risk of bias assessment using the Jadad scale for randomized controlled trials and Newcastle-Ottawa Scale for cohort and case-controlled studies.

Results. Over the 46 years analyzed, the search strategy produced 2904 titles. In total, 314 abstracts were screened, from which 192 full-text articles were evaluated, and 145 research papers met all the criteria for inclusion in the study. Overall, the available evidence was of low quality. Seventy percent of studies (102 of 145) were case reports or case series from which only limited conclusions can be drawn. Only 3% of the included papers (4 of 145) were randomized controlled studies. The remaining data were mainly of a prospective cohort design. Study heterogeneity in design and measured outcomes resulted in data synthesis being limited to a descriptive/exploratory review. Study findings are presented by women’s health category and then by rhinological manifestation with important clinical correlations highlighted.

Conclusion. Physiological and hormonal changes occurring as a normal part of women’s health have an important influence on rhinological function and disease.

Keywords

nose diseases, rhinosinusitis, olfaction disorders, reproductive physiological phenomena, pregnancy complications, menopause, hormone replacement therapy, menstruation disturbances

Received October 29, 2012; revised January 4, 2013; accepted January 17, 2013.

There is a general perception that physiological and hormonal changes associated with various female conditions occurring during a woman’s life span may have an influence on rhinological function and disease. The aim of this review was to systematically identify and appraise the evidence for any such association. We present a descriptive and exploratory review intended to give a broad overview of what has been published rather than a hypothesis-testing undertaking.

Attention was focused on 3 main areas of women’s health: pregnancy and postpartum, menstruation and oral contraceptive pill (OCP), and menopause and hormone replacement therapy (HRT).

Results were analyzed according to their influence on 6 common rhinological conditions: olfaction, epistaxis, rhinitis, rhinosinusitis, nasal tumor, and inflammatory vasculitis.

The rationale for this review was to confirm or refute many frequently held beliefs with regard to how women’s health can affect common rhinological conditions to better tailor management protocols with the physiological changes of women taken into account.

Methods

Protocol and Registration

A study protocol was peer reviewed by the University of British Columbia Division of Otolaryngology Research Committee prior to any search being performed.

1Division of Otolaryngology, Head and Neck Surgery, Children’s and Women’s Hospital, Vancouver, BC, Canada

This article was presented at the 2012 AAO-HNSF Annual Meeting & OTO EXPO; September 9-12, 2012; Washington, DC.

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Eligibility Criteria
A comprehensive search strategy using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was developed to identify any peer-reviewed randomized controlled trials (RCTs), comparative studies, observational studies, case series, or case reports that fulfilled the following inclusion and exclusion criteria.

Inclusion Criteria.
- Humans, female
- Adult (age 19 years and older)
- Primary research studies
- English language
- Publication date from January 1966 to October 2012 (MEDLINE) or January 1980 to October 2012 (EMBASE)
- Original published studies related to rhinological pathology during pregnancy, postpartum, menstruation, menopause, or while taking oral contraceptives or hormone replacement therapy

Exclusion Criteria.
- Review articles with no primary research data
- Animal models or in vitro studies
- Pediatric studies (age 18 years and younger)
- Pregnancy studies about neonatal outcomes rather than the maternal condition
- Olfaction studies with no direct data on nasal pathology
- Olfaction studies related to hedonic outcomes
- Olfaction studies related to congenital anosmia syndromes such as Kallman’s syndrome

Justification for Eligibility Criteria. Given the large scope of this review in terms of broad inclusion criteria over a 46-year period, it was decided to limit the search to English-language primary studies on adults. Similarly, information gathering was confined to the study protocol as outlined, and further manual searches of the references and contacting of experts in the field were not a part of this exploratory review. Olfactory studies reporting hedonic outcomes were excluded due to these being primarily cortical in origin rather than of nasal etiology.

Search Strategy
The above eligibility criteria were applied to 2 medical literature databases: MEDLINE (from January 1966 to October 2012) and EMBASE (from January 1980 to October 2012).


Study Selection
Titles were initially screened to select abstracts that broadly met the inclusion criteria. Two authors screened all of the abstracts independently, and the combined selections were retrieved for full article appraisal. Independent review of each full journal article was undertaken by 2 authors. Duplications and articles not meeting the eligibility criteria after full review were excluded. The remaining studies formed the basis of the review from which data were extracted and risk of bias assessed.

Data Extraction and Analysis
Identified research papers were collated according to the phase of women’s health and the rhinological manifestation under investigation. Key findings and data of interest were summarized for each article. Agreement between studies was noted and disparities explored. Because of the heterogeneous nature of the studies presented and lack of cohesion between methodologies, it was not appropriate to perform any meta-analysis of the data.

Risk of Bias in Individual Studies
Each study was graded as to the level of evidence according to the 2011 criteria set by the Oxford Centre of Evidence Based Medicine. Risk of bias was assessed using established assessment criteria: the Jadad scale was applied to all randomized controlled trials and appraised the quality of randomization according to a 5-point scale. The Newcastle-Ottawa Scale (NOS) was applied to all cohort or case-controlled studies and scored the quality of the study out of a total of 9 points. We considered studies achieving scores of 8 to 9 to be low risk of bias, 6 to 7 medium risk, and scores <6 high risk. All articles were independently assessed with these criteria, and in cases of disagreement, the lower of the two scores was used.

Results
Study Selection
Over the 46 years analyzed, the search strategy produced 2904 titles; 314 abstracts were screened, from which 192 full-text articles were evaluated. In total, 145 research papers met all the criteria for inclusion in the study. Figure 1...
demonstrates the flow diagram of study selection with numbers of studies reviewed and excluded at each stage.

**Overall Study Characteristics**
Study heterogeneity in terms of design and measured outcomes resulted in data extraction being limited to a narrative description of the findings. Meta-analysis was not appropriate for this particular systematic review. **Figure 2** charts the number of studies pertinent to each aspect of the study according to the level of evidence.

**Overall Risk of Bias within Studies**
Overall, the evidence was of low quality. Seventy percent of studies (102 of 145) were case reports or case series
from which only limited conclusions can be drawn. Only 3% of the included articles (4 of 145) were randomized controlled studies\textsuperscript{5-8} (level 2 evidence). The remaining data were mainly of a prospective cohort design. When assessed by the NOS,\textsuperscript{4} the median score was 6 of 9 (mean 6.4/9), which equates to a high to medium risk of bias in most cases. Studies in general lacked adequate patient numbers and demonstrated poor controlling for factors known to affect rhinological outcome such as smoking history.

### Analysis of Studies

#### Pregnancy and Postpartum

**Olfaction.** The largest study to report on olfactory sensitivity during the pregnant period came from the National Geographic Smell Survey,\textsuperscript{9} which surveyed a total of 290,838 women, of whom 13,610 were pregnant. It used a combination of self-reported “sense of smell” plus a scratch-and-sniff card within the magazine. Comparison of discriminatory ability was only significant for 1 of 6 tested odorants, with the pregnant group performing better. Pregnant women rated their sense of smell lower than the nonpregnant group (\(P < .0001\)) (level 2 evidence, NOS score 7/9).

Contrary results were seen in 2 smaller studies, both of which found pregnant women self-rated their olfactory sensitivity as higher than nonpregnant controls.\textsuperscript{10,11} Of 100 pregnant women asked to rate change with the onset of their pregnancy, 61% reported increased sensitivity, 38% no change, and only 1 woman stated a worsening of sense of smell\textsuperscript{10} (level 3 evidence, NOS score 8/9). A similarly designed study\textsuperscript{11} also reported higher self-rated sensitivity in the pregnant cohort (\(P < .001\)) (level 3 evidence, NOS score 7/9). Further details of these studies are represented in Table 1.

Olfactory threshold was examined with serial \(n\)-butanol dilutions in 3 separate studies\textsuperscript{11-13} with mixed results. One study found no significant difference between pregnant and nonpregnant groups\textsuperscript{12} (level 3 evidence, NOS score 8/9), whereas another showed a significant decrease in threshold in the third trimester continuing into the postpartum period\textsuperscript{11} (\(P = .001\)) (level 3 evidence, NOS score 7/9). The third studied whether previous pregnancy and multiparity made a long-lasting influence on threshold and again found no statistical difference\textsuperscript{15} (level 3 evidence, NOS score 8/9).

Identification and discrimination were assessed with the Sniffin’ Stick Test Kit (Heinrich Burghart Elektro-und Feinmechanik GmbH, Wedel, Germany)\textsuperscript{11-13} and the University of Pennsylvania Smell Identification Test (UPSIT).\textsuperscript{10} No significant difference between pregnant and control groups was reported in any of these studies (level 3 evidence). A number of other studies employed poor methodologies, limiting the validity of their results.\textsuperscript{14-17}

Cortical responses to olfactory presentations (chemosensory event related potentials or CSERPs) failed to demonstrate a difference between pregnant and nonpregnant controls\textsuperscript{18} (level 3 evidence, NOS score 6/9).

**Epistaxis.** There were a number of case studies of epistaxis occurring during pregnancy,\textsuperscript{19-24} but several of these were complicated by other contributing comorbid diagnoses such as idiopathic thrombocytopenic purpura\textsuperscript{24} or known coagulopathy.\textsuperscript{22} One large questionnaire-based study\textsuperscript{25} of 1470 pregnancies, which controlled for confounding hemorrhagic conditions, demonstrated a prevalence of 20.3% compared with 6.2% in a nonpregnant control group (\(P < .001\)) (level 2 evidence, NOS score 8/9). Epistaxis was defined as 1 or more “active” nosebleeds during the pregnancy or a similar incidence during the preceding year in the age-matched nonpregnant controls.

**Rhinitis.**

**Pregnancy rhinitis.** Pregnancy rhinitis was poorly defined between studies such that estimation of the true prevalence was difficult to gauge. Bende and Gredmark\textsuperscript{26} performed a large prospective longitudinal study of 2264 pregnant women assessing the likelihood of experiencing daily nasal obstruction for at least 3 weeks at various stages in the pregnancy. They found an increasing prevalence with gestational age, with an overall 65% experiencing nasal obstruction at some stage.

The second largest study looked at 599 pregnancies\textsuperscript{27} and found a prevalence of 22% using a definition of chronic
nasal obstruction not attributable to upper respiratory tract infection or allergy occurring during the last 6 weeks of pregnancy and resolving within 2 weeks postpartum. This definition was common to 6 other studies, giving a mean prevalence of 19.6% with good interstudy agreement (level 2 evidence). See Table 2 for further details of these studies.

Various other durations were used to define the condition in the remaining studies, including 2 weeks, 10 days, and “any complaint of nasal stuffiness,” giving no clear definition was reported in several studies.

Pregnancy rhinitis was generally reported as a separate entity from allergic rhinitis. A well-designed cohort study of 165 pregnant women compared those with and without

### Table 1. Olfaction and Pregnancy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Evidencea (NOS Score)</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported olfactory sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilbert and Wysocki9</td>
<td>1991</td>
<td>290,838</td>
<td>Level 2 (7)</td>
<td>National Geographic Smell Study. Self-rated sense of smell (grade 1-5) on questionnaire incorporated in National Geographic magazine.</td>
<td>Pregnant group rated their sense of smell lower than the nonpregnant group ($P &lt; .0001$).</td>
</tr>
<tr>
<td>Cameron10</td>
<td>2007</td>
<td>100</td>
<td>Level 3 (8)</td>
<td>20 per trimester with 2 control groups (postpartum and nonpregnant). Self-rated sense of smell (grade 1-7) at test time and retrospectively (prepregnancy).</td>
<td>Pregnant groups rated sensitivity higher compared with their prepregnancy rating and with nonpregnant controls ($P &lt; .0001$). Greatest effect in first-trimester group ($P = .01$).</td>
</tr>
<tr>
<td>Ochsenbein-Kolble et al11</td>
<td>2007</td>
<td>84</td>
<td>Level 3 (7)</td>
<td>38 pregnant and 46 nonpregnant women. Self-rated olfactory sensitivity with 10-cm VAS.</td>
<td>Pregnant group rated themselves as more sensitive to odors than did controls ($P &lt; .001$).</td>
</tr>
<tr>
<td>Objectively measured olfactory threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolble et al12</td>
<td>2001</td>
<td>112</td>
<td>Level 3 (8)</td>
<td>Serial $n$-butanol dilution test. 53 pregnant and 59 nonpregnant women. Only studied first trimester.</td>
<td>No significant difference between pregnant and nonpregnant controls.</td>
</tr>
<tr>
<td>Wohlgemuth et al13</td>
<td>2008</td>
<td>93</td>
<td>Level 3 (8)</td>
<td>Serial $n$-butanol dilution test. 26 nulliparous, 26 uniparous, and 41 multiparous participants.</td>
<td>No significant difference between any groups.</td>
</tr>
<tr>
<td>Ochsenbein-Kolble et al11</td>
<td>2007</td>
<td>84</td>
<td>Level 3 (7)</td>
<td>Serial $n$-butanol dilution test. 38 pregnant women analyzed at first, second, and third trimesters and postpartum plus 46 nonpregnant controls.</td>
<td>Decreased threshold (increased sensitivity) seen in pregnant group compared with controls in third trimester ($P = .001$) and postpartum ($P &lt; .001$).</td>
</tr>
<tr>
<td>Objectively measured olfactory identification and discrimination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolble et al12</td>
<td>2001</td>
<td>112</td>
<td>Level 3 (8)</td>
<td>Sniffin’ Stick Test Kit.$b$ 53 pregnant and 59 nonpregnant women. Only studied first trimester.</td>
<td>No significant difference between pregnant and nonpregnant controls.</td>
</tr>
<tr>
<td>Cameron10</td>
<td>2007</td>
<td>100</td>
<td>Level 3 (8)</td>
<td>UPSIT. 20 patients per trimester with 2 control groups (postpartum and nonpregnant).</td>
<td>No significant difference between any groups.</td>
</tr>
<tr>
<td>Wohlgemuth et al13</td>
<td>2008</td>
<td>93</td>
<td>Level 3 (8)</td>
<td>Sniffin’ Stick Test Kit.$b$ 26 nulliparous, 26 uniparous, and 41 multiparous participants.</td>
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<td>No significant difference between pregnant and nonpregnant groups at any stage.</td>
</tr>
</tbody>
</table>

Abbreviations: UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

*aLevel of evidence graded according to the Oxford Centre for Evidence Based Medicine 2011 criteria. NOS score represents the Newcastle-Ottawa Scale of study quality (graded 0-9).

$bSniffin’ Stick Test Kit (Heinrich Burghart Elektro-und Feinmechanik GmbH, Wedel, Germany).
prenatal rhinitis and found no difference in overall seroactivity or hyperreactivity to histamine, concluding that prenatal rhinitis is not an allergic manifestation. Several other studies also reported no correlation between pregnancy rhinitis and pre-pregnancy allergic rhinitis.27,29,35

No correlation was found between pregnancy rhinitis and asthma,27,29 parity,29,35 age,29 child’s sex,29 or estrogen/progesterone levels.31 One study found a significantly higher proportion of smokers in women with pregnancy rhinitis (P = .003)39 (level 3 evidence, NOS score 6/9).

Correlation of these subjective assessments of nasal obstruction with objective measures such as mucociliary flow30 or anterior rhinoscopy32 was poor. One study assessed the histological changes in pregnant women complaining of nasal symptoms38 and found changes similar to those seen in allergic rhinitis.

In terms of treatment for pregnancy rhinitis, there were 2 small but well-designed single-center placebo-controlled double-blinded studies with appropriate outcome measures.5,6 The first trialed an oral decongestant (phenylpropanolamine) vs placebo,6 and the second used topical nasal steroid (fluticasone) vs placebo.5 Neither showed a significant difference in outcome whether by subjective symptom score or objective nasal peak flow or rhinostereometry (level 2 evidence, Jadad score 3/5). Numbers were small but well matched. A possible bias included the unrestricted use of oral antihistamines. The topic of desensitization during pregnancy was studied in an article from 1966, but long-term outcomes were not reported.46

Rhininosinusitis. The reviewed literature contained only case studies (level 4 evidence) with regard to the effect of pregnancy on rhinosinusitis.47-54 The majority reported complications, but as to what contribution the pregnant state made on the disease progression was confounded by other comorbidities in most cases. There were 3 case reports of invasive fungal rhinosinusitis,49,52,53 but again 2 had immunosuppressive comorbidities (diabetic ketoacidosis53 and aplastic anemia49). The third case52 involved fulminant Drechslera spicifera rhinosinusitis in an immunocompetent 21-year-old that presented in the first trimester and rapidly progressed.

The authors postulate that the rapid growth was due in part to the hormonal conditions of the pregnancy.

Nasal Tumor.

Pyogenic granuloma. Pyogenic granuloma was by far the most commonly reported nasal tumor occurring during pregnancy, with 19 isolated case reports or case series.55-73 Almost all cases involved excision of the lesion under local anesthetic with approximately three-quarters of the case studies performing this during the pregnancy and the remainder in the postpartum period. Recurrence was reported in 3 of the 16 cases excised during pregnancy (18.8%). None of the 6 cases of excision within the postpartum period reported recurrence (level 4 evidence).

Other nasal tumors. There were 6 case reports of nasal tumors occurring during pregnancy: Burkitt lymphoma,74 midline lethal granuloma,75 angiofibroma,76 eccrine poroma,77 olfactory neuroblastoma,78 and giant cell granuloma.79 Several of these described rapid growth patterns during the pregnancy attributed to the altered hormonal and immunological conditions74,76,77,79 (level 4 evidence).

Two cases of metastatic choriocarcinoma to the nasal cavity were reported.80,81 Both occurred in nulliparous women, but one had undergone spontaneous abortion 6 months prior80 and the other had a hydatidiform pregnancy 1 year prior81 to the diagnosis of their nasal metastatic disease. Neither was pregnant at the time of the nasal mass.

Vasculitis. Studies involving systemic vasculitis and pregnancy were again solely case report based (level 4 evidence). There were multiple reports of both Wegener’s granulomatosis (WG) and Churg-Strauss vasculitis (CS) occurring de novo during pregnancy,82-93 or the postpartum period.94-99

For patients with a previous established diagnosis of systemic vasculitis subsequently becoming pregnant, approximately half of the case reports (48%) documented a flare-up of the disease,97,99-109 and half were not exacerbated during the time of the pregnancy98,99,110-116 (level 4 evidence).

Menstruation and Oral Contraceptive Pill

There were no studies relating the menstrual cycle or OCP to rhinosinusitis, nasal tumors, or systemic vasculitis.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Evidence (NOS Score)</th>
<th>Definition</th>
<th>Methodology</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bende and Gredmark&lt;sup&gt;26&lt;/sup&gt;</td>
<td>1999</td>
<td>2264</td>
<td>Level 2 (8)</td>
<td>“Daily nasal stuffiness for 3 weeks’ duration”</td>
<td>Prospective longitudinal study over 1 year: Self-reported nasal stuffiness</td>
<td>Prevalence increases with gestational age: 27% (12 wk), 37% (20 wk), 40% (30 wk), and 42% (36 wk). Overall 65% reported “nasal stuffiness”</td>
</tr>
<tr>
<td>Ellegard et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2000</td>
<td>599</td>
<td>Level 2 (8)</td>
<td>“Nasal congestion occurring in the last 6 weeks of pregnancy with no other attributable etiology, resolving within 2 weeks post partum”</td>
<td>Prospective cohort study with nasal congestion assessed by history</td>
<td>22% (95% CI, 19%-26%). Higher incidence in smokers (37% vs 22%) (P = .02). Odds ratio, 1.7 (95% CI, 1.1-2.5). Asthma/hay fever: no correlation</td>
</tr>
<tr>
<td>Shushan et al&lt;sup&gt;32&lt;/sup&gt;</td>
<td>1999</td>
<td>109</td>
<td>Level 2 (7)</td>
<td>“Nasal obstruction and rhinorrhea appearing during pregnancy, lasting at least 2 months and disappearing post partum”</td>
<td>Prospective cohort of women in active labor and 1 month postpartum, assessed by subjective nasal symptoms and anterior rhinoscopy</td>
<td>10/109 (9%)</td>
</tr>
<tr>
<td>Ellegard and Karlsson&lt;sup&gt;28&lt;/sup&gt;</td>
<td>1999</td>
<td>23</td>
<td>Level 3 (6)</td>
<td>“Nasal congestion occurring in the last 6 weeks of pregnancy with no other attributable etiology, resolving within 2 weeks post partum”</td>
<td>Prospective cohort study using subjective symptom score (0-4) and objective nasal peak flow 4 times during pregnancy and postpartum</td>
<td>5/23 (22%)</td>
</tr>
<tr>
<td>Sobol et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>2001</td>
<td>61</td>
<td>Level 3 (5)</td>
<td>No clear definition</td>
<td>Prospective longitudinal study of 33 women (28 nonpregnant controls) using VAS for nasal symptoms during first, second, and third trimesters</td>
<td>“Nasal congestion” in 61%, 55%, and 55% of the pregnant cohort during the first, second, and third trimesters, respectively, compared with 33% of the control group</td>
</tr>
<tr>
<td>Mabry&lt;sup&gt;35&lt;/sup&gt;</td>
<td>1986</td>
<td>66</td>
<td>Level 4 (4)</td>
<td>Loose definition of “constant or frequent nasal congestion” at any time during the pregnancy</td>
<td>Retrospective questionnaire given during the third trimester (ninth month of pregnancy)</td>
<td>12/66 (18%)</td>
</tr>
<tr>
<td>Turnbull et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>1996</td>
<td>160</td>
<td>Level 4 (2)</td>
<td>Poorly defined. “Nasal congestion that was pregnancy related”</td>
<td>In recruitment for a therapeutic device trial, pregnant women were screened for nasal symptoms.</td>
<td>34/160 (21%)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; VAS, visual analog scale.

<sup>2</sup>Level of evidence graded according to the Oxford Centre for Evidence Based Medicine 2011 criteria. <sup>3</sup>NOS score represents the Newcastle-Ottawa Scale of study quality (graded 0-9).
Olfaction. Studies of olfaction with menstruation were generally poorly designed with small numbers and heterogeneity in testing methods.

Threshold analysis used either the Fortunato-Niccolini olfactometer,\textsuperscript{117,118} or dilutional testing of a single vapor: 2-furaldehyde,\textsuperscript{119} exaltolide,\textsuperscript{120} cyclopentadecanolide,\textsuperscript{121} or amyl acetate.\textsuperscript{122} These studies universally found an increased sensitivity (lowest threshold) at ovulation\textsuperscript{117-122} (level 2 evidence). A number of other studies had such small patient numbers or poor design that the validity of any conclusions was questionable.\textsuperscript{123-125}

Cortical responses to olfactory presentations (CSERPs) did not show the same peak at ovulation but suffered from a sample size of only 6 patients\textsuperscript{126} (level 4 evidence).

There were no studies of olfactory identification or discrimination ability with regard to menstruation or OCP.

Epistaxis. There were no studies on epistaxis and the menstrual cycle and only 1 case report of a woman taking the OCP for 6 months who then had an episode of severe epistaxis.\textsuperscript{127} A case series of 4 patients with hereditary hemorrhagic telangiectasia all taking the OCP\textsuperscript{128} postulated that it may have increased the frequency of epistaxis, but the findings were poorly supported by any substantial data (level 4 evidence).

Rhinitis. A large single-cohort study of 4077 menstruating women found an increased prevalence of allergic rhinitis with irregular menstruation vs regular menstruation (28.8% vs 23.6%; odds ratio, 1.29; 95% CI, 1.05-1.57)\textsuperscript{129} (level 2 evidence). However, diagnosis of allergic rhinitis was by subjective response to a single question regarding “hay fever or nasal allergies” on a postal questionnaire.

Association was also demonstrated with premenstrual syndrome (PMS) in a moderate-sized cohort study in which the prevalence of physician-diagnosed allergic rhinitis was compared in patients diagnosed with PMS with age-matched female controls.\textsuperscript{130} The group with a diagnosis of PMS had a 29.5% prevalence of allergic rhinitis compared with only 15.2% of women without PMS (odds ratio, 2.33; 95% CI, 1.13-4.86; \( P < .02 \)) (level 2 evidence).

Although 8 articles\textsuperscript{117-119,131-135} studied the effects of the menstrual cycle on nasal physiology, most were small, and a variety of methodologies were used. The largest study (reported separately in the rhinology and reproductive literature) employed rhinomanometry and found no significant difference between phases of the menstrual cycle\textsuperscript{117,118} (level 2 evidence, NOS score 9/9). Other smaller studies using rhinomanometry had mixed results, 1 also finding no significance\textsuperscript{131} but 2 finding increased nasal resistance at mid-cycle.\textsuperscript{119,132} Acoustic rhinometry failed to show a statistically significant difference in nasal volume during the menstrual cycle\textsuperscript{132,133,135} (level 3 evidence). Nasal peak flow suggested significantly increased resistance at menstruation, which correlated well with subjective scoring\textsuperscript{134} (level 3 evidence, NOS score 8/9). Table 3 outlines the detail of these studies.

One small longitudinal study of 11 women looked at various nasal physiological parameters before and during use of the OCP and found no significant changes in nasal peak flow, acoustic rhinometry, rhinomanometry, or mucociliary flow\textsuperscript{136} (level 4 evidence). This was complemented by another small cohort study that found no difference in rhinomanometry measurements between women taking the OCP and matched controls\textsuperscript{137} (level 2 evidence, NOS score 5/9).

Two histological studies of the nasal mucosa attributed changes to the varying levels of estrogen.\textsuperscript{138,139} Smear cytology showed increased cornified cells during the follicular phase, which mirrored changes seen in menopause and prepubertal conditions.\textsuperscript{138} Symptomatic patients using the OCP had changes of squamous metaplasia, glandular hyperplasia, interstitial edema, and fibrous tissue deposition.\textsuperscript{139}

Menopause and Hormone Replacement Therapy

There were no studies found that analyzed menopause or HRT and rhinosinusitis, nasal tumors, or systemic vasculitis.

Olfaction. In a cohort study of 62 postmenopausal women, half of whom had self-selected to take HRT, no significant difference was reported in threshold detection or UPSIT-measured discrimination\textsuperscript{140} (level 3 evidence, NOS score 7/9). However, a longitudinal study of 47 women, using the Fortunato-Niccolini olfactometer to measure olfactory threshold before and during HRT use, did show a significant improvement in sensitivity after 6 cycles of HRT (\( P < .001 \))\textsuperscript{141} (level 2 evidence, NOS score 9/9).

Deems et al\textsuperscript{142} looked at a large cohort presenting with olfactory dysfunction, including 414 women, of whom 99 were postmenopausal. Performance of pre- vs postmenopause subgroups was not reported, but they did speculate that HRT may preserve olfactory function because only 4 of the 99 menopausal women were on HRT, which is statistically fewer than reported in other studies (4% vs 16%; \( P < .001 \)). Performance of the HRT group demonstrated no difference in threshold detection but an increased performance on UPSIT (\( P < .005 \)) (level 2 evidence, NOS score 6/9). This suffers from the fact that the HRT arm had only 4 patients.

Several studies whose primary outcomes related to other pathologies such as Alzheimer’s dementia\textsuperscript{143,144} or schizophrenia\textsuperscript{145} indirectly reported information with regard to the role of menopause or HRT on olfaction. Of these studies, no significant difference was seen in threshold\textsuperscript{144} or UPSIT-measured discrimination\textsuperscript{143} with patients taking HRT. With regard to menopause, extrapolating the data from menopause subgroups of a study of schizophrenia patients\textsuperscript{145} found lower UPSIT-measured discrimination scores in the postmenopausal groups (\( P = .01 \)), which correlated well with measured estradiol assays.

Epistaxis. A large French study of 2197 mature-aged women,\textsuperscript{146} of whom 74% were postmenopausal, reported a yearly incidence of epistaxis of 7.6%, which required medical attention in <4% of cases. This figure did not control for those on HRT (69%) plus may have been biased by the
entire cohort being enrolled in a trial of an oral antioxidant supplement that could perceivably affect nasal bleeding.

A small longitudinal study of patients diagnosed with hereditary hemorrhagic telangiectasia before and after 6 months’ use of HRT found a significant decrease in Sadich epistaxis scores following HRT use147 (level 3 evidence, NOS score 5/9).

Rhinitis. Several large questionnaire-style cross-sectional studies looked at the incidence of rhinitis symptoms in mature-aged women. In the French antioxidant supplement cohort mentioned above, the authors also studied rhinitis symptoms.146 They found that a statistically higher proportion of postmenopausal patients reported at least 1 symptom of rhinitis in a 1-year period (71.3% vs 64.1%; odds ratio, 1.47; 95% CI, 1.2-1.9), whereas no significant difference was evident in those taking HRT (level 2 evidence).

A UK questionnaire-based survey of 3724 women148 found significantly higher reporting of rhinitis symptoms in the postmenopausal subgroup (odds ratio, 1.28; 95% CI, 1.07-1.76). Increased reporting was also seen in HRT vs non-HRT use, but this only reached significance in the age group older than 55 years (odds ratio, 1.58; 95% CI, 1.11-2.23) (level 2 evidence).

A similar Scandinavian survey of 1527 women,149 of whom 424 were postmenopausal and not taking HRT, found no difference in the reporting of “hay fever or nasal allergy” symptoms (level 2 evidence). They noted an increased reporting of such symptoms in those using HRT (odds ratio, 1.47; 95% CI, 1.14-1.88), but the non-HRT arm contained all the premenopausal patients, which might have affected the outcome.

Studies using objective measures of nasal function in patients on HRT all suffered from low patient numbers.141,150,151 One randomized nonblinded placebo-controlled approach149 had treatment arms of only 12 patients but reported significant changes in both subjective score and mucociliary transit time for the HRT group (P < .01 and P < .05, respectively). Rhinomanometry-measured airway resistance remained unchanged (level 3 evidence, Jadad score 4/5).

Two longitudinal studies of patients before and during HRT had opposing conclusions. Caruso et al141 found improvement in nasal resistance following HRT use (P < .001) in a cohort of 47 menopausal women (level 2 evidence, NOS score 9/9), whereas a second smaller study of 20 patients,151 which in addition measured nasal peak flow, acoustic rhinometry, and mucociliary flow, found no significant difference in any variable (level 3 evidence, NOS score 5/9). However, controlling of confounding factors was poor, and they employed a variable end point ranging from 77 to 195 days of HRT.

Discussion

The effect of pregnancy on olfaction appears limited. Pregnant women’s perception that their sensitivity changes,
which varied between studies as to whether it increased\textsuperscript{10,11} or decreased,\textsuperscript{9} was not supported by objective studies of olfactory threshold or discrimination, which tended to show no significant difference between pregnant and nonpregnant olfactory performance\textsuperscript{10-13} (level 2 evidence).

The effect of menstruation appeared more conclusive, with several studies in agreement that olfactory sensitivity peaks at ovulation\textsuperscript{117-122} (level 2 evidence).

The belief that HRT may preserve olfactory sensitivity was not convincingly demonstrated in the literature, with roughly equal numbers of studies reporting opposing conclusions in this regard. However, the 1 well-designed longitudinal study with the lowest risk of bias did suggest that thresholds improved after establishment of HRT\textsuperscript{141} (level 2 evidence).

The widely held view that epistaxis is more frequent during pregnancy was demonstrated in at least 1 well-designed study,\textsuperscript{25} whereas the effects of the menstrual cycle or oral contraceptive were not conclusive. Menopause again demonstrated a rise in prevalence but more modest than that seen in pregnancy.\textsuperscript{146} (level 2 evidence).

The existence of a form of rhinitis specific to pregnancy was reported in a number of studies, but there was a lack of cohesion in terms of the definition of what qualifies such a diagnosis. Given the common definition of late pregnancy onset (last 6 weeks) of persistent rhinitis in a previously asymptomatic patient that resolves within 2 weeks postpartum, the prevalence would appear to be approximately 1 in 5 pregnancies\textsuperscript{28-32} (level 2 evidence). Other than a tentative link with smoking,\textsuperscript{29} there were no other obvious risk factors.\textsuperscript{27,29,31,35} It is interesting that no improved outcome was demonstrated with the use of topical nasal steroids\textsuperscript{6} (level 2 evidence), but it is worth remembering that all cases, by definition, resolve following birth.

Allergic rhinitis appears no more prevalent in pregnancy than in nonpregnant populations\textsuperscript{39-41} but may reduce with multiparity.\textsuperscript{54} There were some data to support that irregular menstruation and premenopausal syndrome are associated with an increased prevalence of rhinitis,\textsuperscript{129,130} but objective data on the influence of the cycle itself on nasal physiology were mixed.\textsuperscript{117-119,131-134} The use of OCP does not appear to affect nasal airflow,\textsuperscript{136,137} but studies had a high risk of bias. The effect of menopause on nasal allergic symptoms was not conclusive, with 3 large population studies disagreeing.\textsuperscript{146,148,149} Objective measures of nasal airflow with HRT use displayed similarly mixed outcomes and were inconclusive.\textsuperscript{141,150,151}

The literature contains several interesting reports of pregnancies affected by complications of rhinosinusitis, but the influence of the pregnancy itself on the clinical course of the disease is speculative at best, with most cases having other contributing factors.\textsuperscript{47-54}

The general conception that pyogenic granuloma is the commonest nasal mass found in pregnancy was certainly supported by the large number of case reports in the literature.\textsuperscript{55-73} Inferences can be made from this with regard to the recurrence rate after excision, which appears to approximate 1 in 5 (level 4 evidence). There is tentative evidence to support the notion that excision in the postpartum period pertains to a lower likelihood of recurrence (level 4 evidence).

Multiple studies reported de novo occurrence of systemic vasculitis presenting with nasal manifestations during pregnancy and postpartum\textsuperscript{82-99} such that this differential should always be kept in mind when assessing the pregnant patient with atypical nasal symptoms. The influence of pregnancy on established cases of systemic vasculitis was not clear, but a significant proportion did experience exacerbations.\textsuperscript{97,99-109}

Although this exploratory review was limited to the English language and did not incorporate manual searches or expert opinion, it still remains a comprehensive assessment of the literature to date and highlights the multiple deficits that exist in this field. Without doubt, further research is required to fully delineate the exact relationship of several of these female physiological conditions with the rhinological manifestations presented. Future studies should ensure that adequate patient numbers are recruited to make their conclusions meaningful and ensure standardized definitions or diagnostic criteria are applied, especially in the area of pregnancy rhinitis. A more stringent study design in terms of adequate controlling for conditions affecting nasal physiology such as smoking plus ensuring adequate numbers in control groups would help to resolve many of the unanswered questions in this interesting field.

Acknowledgments

We thank the senior librarian, Karen MacDonell, at the College of Physicians and Surgeons of British Columbia Library for her assistance with creating a search protocol for this study.

Author Contributions

Alexander J. Saxby, read and analyzed all papers in review and wrote paper; Pia Pace-Asciak, read and analyzed all studies in systematic review and gave oral presentation at AAO-HNSF meeting; Rachelle C. Dar Santos, involved in study design and acquisition of all studies to be reviewed and critical appraisal of drafted report; Neil K. Chadha, involved in study design and critical appraisal of drafted report; Frederick K. Kozak, involved in study design and selected all titles for full reference review and critical appraisal of drafted report.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: None.

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