

**Management of Rhinosinusitis During Pregnancy:  
Systematic Review and Expert Panel Recommendations**

A thesis submitted to the University of Arizona College of Medicine – Phoenix  
in partial fulfillment of the requirements for the degree of Doctor of Medicine

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Class of 2016

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**Acknowledgements:**

I would like to acknowledge my mentor Dr. Devyani Lal. Dr. Lal's guidance has been invaluable and my thesis would have been impossible without it. I would also like to thank Kathleen Carlson for her guidance as I began this project. Finally I would like to thank Dr. James Stanciewicz, Dr. Valerie Lund, Dr. Peter Hwang, Dr. Matthew A. Rank, Dr. Larry Borish, and Dr. Linda Chambliss for their contributions to this project.

**Abstract:**

**Background:** Rhinosinusitis, both acute and chronic, represents a common disease.

Approximately 29.6 million adults in the United States suffer from sinusitis with 11 million suffering from CRS<sup>1</sup>. The multicenter GA2LEN study showed that amongst lifetime nonsmokers, women were at a greater risk of being affected by chronic rhinosinusitis than men<sup>2</sup>. Various other rhinologic manifestations of pregnancy have also been described. Nevertheless, management of rhinosinusitis during pregnancy is poorly described in the literature.

**Objectives:**

1. Conduct a systematic review of the literature for the management of acute and chronic rhinosinusitis (CRS) during pregnancy.
2. Make evidence based recommendations on the management of acute and chronic rhinosinusitis during pregnancy.

**Methods:** A systematic review of the literature was conducted using MEDLINE and EMBASE databases. Search terms included “rhinitis” OR “sinusitis” OR “rhinosinusitis” AND “pregnant” OR “women” OR “gender”. Title, abstract, and full manuscript review was conducted. Full manuscripts including citations and references were reviewed if the abstract noted any gender specific outcomes. A multispecialty panel of experts in the fields of rhinology, allergy-immunology, and obstetrics-gynecology was invited to review the systematic review. Recommendations were sought on the use of the following for the management of CRS during pregnancy: oral corticosteroids, antibiotics, leukotriene antagonists, topical corticosteroid sprays/irrigations/drops, aspirin desensitization, elective surgery for CRS, and vaginal birth vs. planned cesarean delivery for patients with history of skull base erosions or CSF rhinorrhea.

**Results:** 3052 abstracts were screened, and 88 manuscripts were reviewed. No relevant level 1, 2 or 3 studies were found. Expert panel recommendations were synthesized.

**Conclusions:** Several recommendations were made. These include continuing all modern topical corticosteroids for CRS maintenance, using pregnancy safe antibiotics for acute rhinosinusitis and CRS exacerbations, and discontinuing aspirin therapy for desensitization in patients with aspirin exacerbated respiratory disease.

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## **Introduction and Significance:**

Approximately 29.6 million adults in the United States suffer from sinusitis, with 11 million suffering from chronic rhinosinusitis<sup>1</sup>. The multicenter GA2LEN study showed that amongst lifetime nonsmokers, women were at greater risk of being affected by CRS than men<sup>2</sup>. Pregnancy itself represents a unique physiological state with known hormonal effects on the sinonasal mucosa<sup>3,4</sup>. Additionally, labor has been associated with increases in cerebrospinal fluid (CSF) pressures<sup>5</sup>, raising potential for concern in patients with a history of skull base erosions or CSF leaks.

Various rhinologic manifestations of pregnancy have also been described. The commonly discussed conditions include rhinitis of pregnancy, epistaxis, and certain tumors such as pyogenic granuloma<sup>6-10</sup>. Sporadic case reports also describe complications that may arise from rhinosinusitis during pregnancy<sup>11,12</sup>. As such special considerations must be taken during the management of rhinosinusitis during pregnancy, considerations that account for both maternal and fetal health. However, management of rhinosinusitis during pregnancy is poorly described in the literature<sup>6</sup>. Furthermore, clinical practice guidelines on chronic rhinosinusitis from the American Academy of Otolaryngology-Head & Neck Surgery and the European Rhinologic Society also do not offer structured guidelines to Otolaryngologists on managing rhinosinusitis in the pregnant patient<sup>13,14</sup>. Therefore there is a need for reviewing the literature to examine the evidence for managing rhinosinusitis and its associated comorbidities during pregnancy.

Here we study management of rhinosinusitis during pregnancy so as to provide recommendations for evidence based management and best practices.

## **Materials and Methods:**

### **Systematic Review and Search Strategy:**

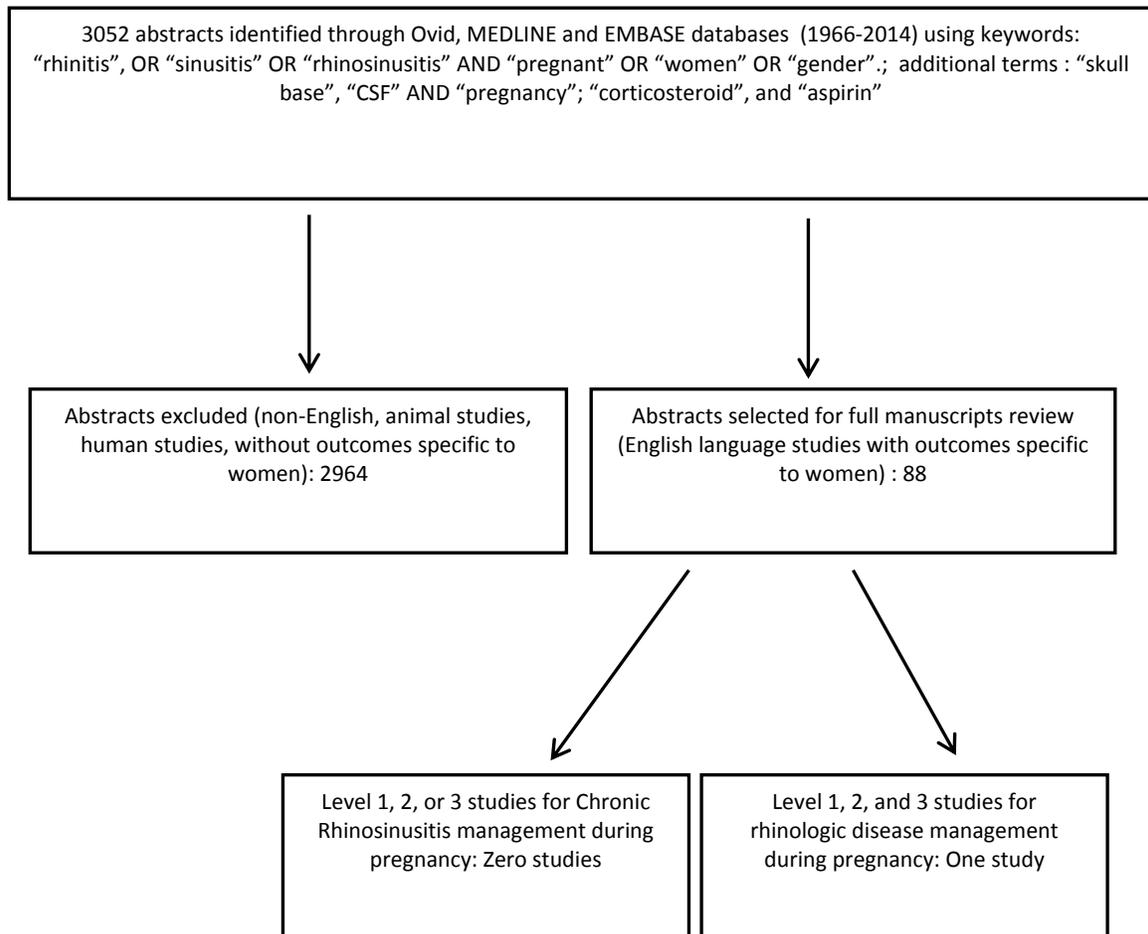
A systematic review of the English language literature was conducted using the MEDLINE (1966-2014) and EMBASE (1980-2014) databases. The search titles, abstract screening, and full manuscript review was conducted. The level of evidence was graded according to the Oxford Centre of Evidence Based Medicine 2009 criteria<sup>15</sup>.

A comprehensive search strategy using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was developed (figure 1). Randomized controlled trials (RCTs), comparative studies, observational studies, case series, and case reports were evaluated for eligibility. Studies related to rhinitis and rhinosinusitis were both evaluated, as these conditions may be difficult to distinguish in the absence of radiologic testing (computerized tomography) or rhinoscopy. Studies that comprised primary research on pregnant human females were included. Studies were excluded if they consisted of animal or *in vitro* research. Studies were also excluded if they were review articles with no primary research data.

The search strategy was chosen in consultation with a senior librarian at the Mayo Clinic and at the University of Arizona: Arizona Health Sciences Library. The search strategy was as follows: "pregnancy" [MeSH] AND "female" [MeSH] OR "gender" [MeSH] OR "sinusitis" [MeSH] OR sinusitis OR "rhinitis" [MeSH] OR "rhinosinusitis" [MeSH] OR "corticosteroid" [MeSH] OR "corticosteroids" [MeSH] OR "cerebrospinal fluid" OR "CSF" [MeSH] OR "skull Base" [MeSH] OR "aspirin" [MeSH]. English language publications from January 1966 to December 2014 (MEDLINE) or January 1988 to December 2014 (EMBASE) were scrutinized. The search titles were initially screened to select abstracts that broadly met inclusion criteria. Next, full manuscripts were retrieved based on this independent review and again reviewed. Additional studies were included for review based on the references and citations of the full manuscripts. Duplicated articles and those not meeting study criteria after full review were excluded.

**Figure 1:**

Search methodology and Results of the Systematic Review



**Synthesis of Expert Panel Recommendations:**

An international, multidisciplinary expert panel was then created. Experts from the fields of Rhinology, Allergy-Immunology, and Obstetrics-Gynecology were invited. They were selected based upon their expertise in a) systematic reviews and evidence based management of rhinosinusitis, its complications, and medico-legal aspects, b) expertise in the medications/therapeutics of CRS, allergy & asthma, as well as in c) obstetrics & perinatal issues. Each expert was provided with the full results of the systematic review and asked to provide their input and expertise on specific questions (table 1). These expert opinions were then reviewed and synthesized into expert panel recommendations. Next, these recommendations were shared with all experts, collectively and iteratively reviewed and a final expert panel opinion was formalized. Ultimately the final expert panel included four Rhinologists, two experts in Allergy and Immunology and an expert in Maternal and Fetal Medicine.

**Table 1:** Questions presented to experts with regard to CRS management during pregnancy

<b>Question #</b>	<b>Clinical Question</b>
<b>1</b>	Use of oral corticosteroids for CRS exacerbations during pregnancy?
<b>2</b>	Use of topical corticosteroids for CRS maintenance therapy during pregnancy?
<b>3</b>	Use of oral antibiotics for acute rhinosinusitis, acute exacerbations of CRS, and CRS maintenance during pregnancy?
<b>4</b>	Use of anti-leukotrienes for CRS maintenance therapy in the pregnant patient?
<b>5</b>	Use of systemic and topical decongestants, antihistamines and immunotherapy for CRS management in pregnancy?
<b>6</b>	What "Routine" maintenance therapy do you recommend for CRS during pregnancy?
<b>7</b>	Aspirin desensitization therapy during pregnancy for aspirin exacerbated respiratory disease (AERD)?
<b>8</b>	Vaginal Births versus planned Caesarian section for those with large skull base erosions secondary to CRS, secondary to skull base resection, or patients with benign intracranial HTN with history of CSF rhinorrhea?
<b>9</b>	Performance of sinus surgery in patients with recurrent, recalcitrant CRS with polyps prior to conception of a planned pregnancy?

**Results:****Results Summary:**

The literature search yielded 3052 abstracts. After initial screening, 88 full manuscripts were reviewed. No studies related to CRS management during pregnancy that were levels 1, 2, or 3 were found. A two-author, single expert opinion on management of rhinologic disease during pregnancy was found<sup>8</sup>. Given the lack of any studies on the management of RS or CRS during pregnancy, expert panel recommendations were synthesized and are presented below. Table 2 presents the pregnancy risk categories for therapeutic agents.

**Expert Panel Recommendations:****1. Use of oral corticosteroids for CRS exacerbations during pregnancy?****Evidence Level:**

Zero; no studies found; one review article outlined the pregnancy risks associated with antibiotics, antihistamines, decongestants, and intranasal steroids.

**Expert Panel Recommendations:**

Corticosteroids (CCS) in short bursts may be safe after the first trimester. Use is better justified in severe CRS, especially if causing exacerbation of asthma. Consultation with patient's obstetrician is recommended.

**Underlying Values & Preferences:**

Places high value on maternal and fetal safety over sinonasal symptom control

**Remarks:**

Based upon the asthma literature, oral CCS use would be expected to be associated with slightly increased risk for cleft lip with or without cleft palate<sup>16</sup>, increased incidence of preeclampsia, and the delivery of both preterm and low birth weight infants<sup>17,18</sup>. The risks of CCS use are outweighed by risks of undertreated asthma, but this justification is less so in CRS and clinical judgment must be exercised. First trimester use has the greatest risk of potential teratogenicity. CCS cause hyperglycemia and can lead to/worsen diabetes, causing additional maternal-fetal risks. Patients should undergo diabetes testing prior to use, especially if a longer course of corticosteroids is being considered. The American Academy of Pediatrics considers oral steroids to be compatible with breastfeeding.

## **2. Use of topical corticosteroids for CRS maintenance therapy during pregnancy?**

### **Evidence Level:**

Zero; no studies on topical nasal steroids for CRS during pregnancy.

### **Expert Panel Recommendations:**

All modern nasal CCS should be safe to use for CRS maintenance during pregnancy at recommended doses including budesonide, fluticasone and mometasone. The off-label use of budesonide irrigations or CCS nasal drops is not recommended.

### **Underlying Values & preferences:**

Places value on maternal sinonasal inflammation control and quality of life during pregnancy while prioritizing fetal safety.

### **Remarks:**

The only study of nasal corticosteroid spray use in pregnancy, conducted by Ellegard, et al., evaluated fluticasone propionate nasal sprays in 53 women with pregnancy rhinitis in a placebo-controlled randomized study<sup>19</sup>. Daily symptom scores and nasal peak expiratory flow, as well as acoustic rhinometry before and after treatment did not show any differences between the groups. No detectable influence on maternal cortisol as measured by morning S-cortisol and overnight 12-h-U-cortisol, or any difference in ultrasound measures of fetal growth or pregnancy outcome were reported. Another study was a single non-controlled, non-blinded case series of 21 patients who were given 27 intranasal injections of triamcinolone acetonide or prednisolone terburate for severe nasal obstruction during pregnancy<sup>20</sup>. In this, Mabry reported symptom improvement, but there was no study of systemic CCS absorption or pregnancy outcomes. There is fairly good evidence for the safety of inhaled CCS in asthma during pregnancy<sup>21-23</sup>. Budesonide is category B in pregnancy and remains the agent for which the preponderance of safety data exists<sup>24</sup>. Newer generation sprays have negligible systemic absorption and may be safe to use, but evidence that these medications during pregnancy are not associated with any untoward risks is lacking. This applies to usual pharmacologic doses. Budesonide is most widely studied; 50 micrograms in each nostril once or twice daily should be safe to use for CRS maintenance during pregnancy. Whether this extends to higher

doses/potency steroids (e.g., 500 µg budesonide or dexamethasone) applied as nasal drops (in Mygind's position) is unknown.

### **3. Use of oral antibiotics for acute rhinosinusitis, acute exacerbations of CRS, and CRS maintenance during pregnancy?**

#### **Evidence Level:**

Zero; no studies on antibiotics for acute rhinosinusitis (ARS), acute exacerbations of CRS, and CRS maintenance.

#### **Expert Panel Recommendations:**

Oral antibiotics that do not harm the fetus may be used for ARS or acute exacerbations of CRS. Long-term macrolide or doxycycline use for CRS is not recommended during pregnancy. Penicillin and cephalosporin are the safest classes, and can be given when endoscopic evidence of purulence is present. Antibiotics that put the fetus at risk such as tetracyclines, aminoglycosides, trimethoprim-sulfamethaxazole and fluoroquinolones should not be used during pregnancy<sup>25</sup>.

#### **Underlying Values & Preferences:**

Prioritizes fetal and maternal safety and places high value on appropriate treatment of bacterial rhinosinusitis.

### **4. Anti-leukotriene medical therapy in CRS?**

#### **Evidence Level:**

Zero; no studies on CRS.

#### **Expert Panel Recommendations:**

Avoid anti-leukotrienes for CRS maintenance during pregnancy. However, montelukast can be continued/ initiated for recalcitrant asthma during pregnancy, especially in those with prior response.

#### **Underlying Values & preferences:**

Places high value on fetal and maternal safety

#### **Remarks:**

Given the lack of data regarding the efficacy of these drugs in CRS and lack of data regarding teratogenicity, the consensus of this panel was to avoid these drugs in treating CRS.

Montelukast is not teratogenic in animals and the American Congress of Obstetricians and Gynecologists and the American College of Allergy recommend that it could be considered in recalcitrant asthma if the patient has shown a favorable response prior to pregnancy.

Montelukast is a pregnancy category B drug and the manufacturer maintains a registry for patients who are exposed to montelukast in pregnancy. Montelukast is excreted in breast milk and there are no data on what this potential exposure could do to a nursing infant. However, the extensive metabolism and plasma protein binding are thought to limit exposure. About 1% of the drug passes into breast milk, and the benefits of breastfeeding overwhelm the risk of exposure. An additional consideration is to breastfeed prior to intake of medications to further limit exposure. 5-lipoxygenase inhibitors should be avoided in both pregnant and lactating mothers<sup>26</sup>.

## **5. Use of systemic and topical decongestants, antihistamines and immunotherapy for CRS management in pregnancy?**

### **Evidence Level:**

Zero; no studies on CRS.

### **Expert Panel Recommendations:**

Oral decongestants should not be used. First-generation antihistamines should be avoided given their sedative and anticholinergic properties. Allergen immunotherapy is likely safe to continue during pregnancy. However, initiation or buildup of immunotherapy should be not be conducted during pregnancy.

### **Underlying Values & preferences:**

Prioritizes fetal and maternal safety over simple sinonasal symptom control.

### **Remarks:**

No studies assessed these drugs in CRS. Oral decongestants may increase the risk of fetal gastroschisis, and also contribute to hypertension<sup>27</sup>. Decongestants are also not effective in treating CRS. Toll et al. conducted an RCT of phenylpropanolamine for the treatment of

pregnancy rhinitis<sup>28</sup>. They reported that it was more effective than placebo in treating the symptoms of patients. However, there was no difference in rhinometry. This study reported no adverse outcomes but did not report any fetal outcomes. It should be noted that phenylpropanolamine has been withdrawn from the US market. The greatest concern regarding allergen immunotherapy is the risk of anaphylaxis. Sublingual immunotherapy is also generally contraindicated during pregnancy<sup>29</sup>. Current recommendations for AR and asthma are that immunotherapy should be continued at the same dose but should not either be initiated nor should doses be increased during pregnancy.

## **6. What “Routine” maintenance therapy is recommended for CRS during pregnancy?**

### **Evidence Level:**

Zero; no studies on CRS “maintenance” therapy in pregnancy.

### **Expert Panel Recommendations:**

Saline nasal rinses and a topical CCS nasal spray are likely suitable maintenance therapy for CRS during pregnancy.

### **Underlying Values & preferences:**

Prioritizes fetal and maternal safety with value also placed to maternal quality of life and control of sinonasal inflammation.

### **Remarks:**

Studies in allergic rhinitis during pregnancy find saline nasal lavage and nasal CCS sprays safe and effective<sup>14,30</sup>.

## **7. Aspirin therapy for aspirin exacerbated respiratory disease (AERD)?**

### **Evidence Level:**

Zero; no studies on AERD during pregnancy.

### **Expert Panel Recommendations:**

Aspirin therapy for AERD should be discontinued during pregnancy.

### **Underlying Values & preferences:**

Places high value on fetal and maternal safety.

**Remarks:**

Aspirin is considered category D in pregnancy and should be avoided. Aspirin and other NSAIDs pose unacceptable fetal risks, particularly premature closure of the ductus arteriosus. Aspirin itself has also been associated with intrauterine growth restriction and perinatal mortality. Patients who have previously been desensitized and are on maintenance aspirin therapy should discontinue aspirin prior to a planned pregnancy or as soon as possible after becoming pregnant.

**8. Vaginal Births versus planned Caesarian section for those with large skull base erosions secondary to CRS, secondary to skull base resection, or patients with benign intracranial HTN with history of CSF rhinorrhea?****Evidence Level:**

Zero; no relevant studies.

**Expert Panel Recommendations:**

Skull base erosions such as those discussed above are not contraindications for a normal delivery. Generally speaking, cesarean section should be reserved for the standard obstetric indications. However, a highly individualized approach must be undertaken, and ultimately the patient and the obstetrician should determine the route of delivery. The risks of intrapartum CSF leak may be much higher in large skull base resections for malignancies, rather than limited defects from CRS or standard transsphenoidal pituitary tumor resections.

**Underlying Values & preferences:**

Places high value on fetal and maternal safety.

**Remarks:**

One study from 1961 measured CSF pressures during labor and obstetric anesthesia and some case reports of intrapartum CSF leaks were also found<sup>5,31</sup>.

**9. Performance of sinus surgery in patients with recurrent, recalcitrant CRS with polyps prior to planned pregnancy?****Evidence Level:**

Zero; no relevant studies.

**Expert Panel Recommendations:**

Surgery may be considered prior to the pregnancy. In general, surgery that is not for a life threatening process should be avoided during pregnancy. Emergency surgery for complicated and acute/chronic sinusitis may be done with close anesthesia supervision. However, office procedures under local anesthesia may be some helpful alternatives in severely symptomatic CRS pregnant patients. These include polypectomy, indicated balloon sinuplasty, and turbinate surgery under local anesthesia.

**Underlying Values & preferences:**

Prioritizes fetal safety; value also placed to maternal quality of life.

**Discussion:**

This comprehensive systematic review did not find any level 1, 2, or 3 studies specific to the management of rhinosinusitis during pregnancy. While studies show an increase in sinonasal and rhinologic symptoms during pregnancy, there are no studies on the evolution of CRS during pregnancy. This is a substantial gap in our knowledge of the disease process during pregnancy, as well as in our ability to manage pregnancy patients with CRS. Given that RS is believed to be more prevalent in females, and may affect them during childbearing years, it is necessary to conduct relevant studies. Conducting interventional studies in pregnancy is fraught with medical and ethical dilemmas. Therefore, future work in this arena may be done by conducting large population-based studies, such as those seen in the asthma literature.

Given the lack of interventional studies on management of RS during pregnancy, we found it necessary to generate expert panel recommendations (Level 5 evidence) to help guide management. Our multi-disciplinary panel of experts weighed the strength of evidence regarding specific interventions while balancing maternal health against potential fetal risks. These recommendations were given very careful consideration. Nevertheless, given the lack of high quality objective evidence, these are Grade D recommendations. These must be utilized and modified as determined after careful and thoughtful, individualized review of the pregnant patient, and in consultation with their Obstetrician.

**Conclusions:**

Rhinosinusitis is a common condition and women are at an increased risk of suffering from chronic rhinosinusitis. Pregnancy has several rhinologic manifestations and has been associated with worsening of sinonasal symptoms. Despite this, there is a paucity of evidence regarding the management of rhinosinusitis during pregnancy. This study presents a systematic review of the literature on the management of rhinosinusitis during pregnancy and presents an expert panel opinion regarding specific interventions for the management of CRS during pregnancy.

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women. Or, Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect, or no animal studies have been conducted, and there are no adequate and well-controlled studies in pregnant women.
D	Adequate, well-controlled, or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Adequate, well-controlled, or observational studies in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

**Table 2:** Categories of Pharmaceutical Agents Assessing Risk for Use in Pregnancy<sup>32</sup>

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