

Therapy of Recurrent Aphthous Stomatitis in Pregnant Patients

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Abstract

Recurrent aphthous stomatitis or recurrent aphthous ulcerations are ulcerative lesions of the oral mucosa of unknown etiology, with varying prevalence. Due to the recurrent nature of these lesions, it is possible that the true prevalence of recurrent aphthous stomatitis is greater than that reported.

Therapeutic options include treatment with topical or systemic glucocorticoid, immunosuppressant, antimicrobial or anti-inflammatory therapy. During pregnancy, exposure to some drugs may adversely affect the fetus so the objective of this article is to discuss available therapeutic options for recurrent aphthous stomatitis in pregnancy. PubMed database was searched for full-text articles in English language, with key words "recurrent aphthous ulcerations" and "recurrent aphthous stomatitis treatment" and "recurrent aphthous stomatitis in pregnancy". For some agents, data for topical use in humans are limited so pregnancy recommendations are given only for systemic intake. Pregnancy risk categories have been determined by Food and Drug Administration and they represent differences in the degrees of a fetal risk regarding use of a specific drug during pregnancy. Pregnant patients with RAS should be informed about the risk level of the potential drug for the fetus so that they can actively participate in the decision about the treatment. Topical therapy is the therapy of choice. It is effective in most cases and has well-tolerable side-effects.

Keywords: Stomatitis; Aphthous; Ulcerations; Recurrent Aphthous; Therapy; Pregnancy; Risk

Abbreviation

RAS: Recurrent Aphthous Stomatitis

Introduction

Recurrent aphthous stomatitis (RAS) or recurrent aphthous ulcerations are ulcerative lesions of the oral mucosa of unknown etiology. The prevalence of RAS in general population varies between 5% and 25%. Due to the recurrent nature of these lesions, it is possible that the true prevalence of RAS is greater than that reported [1].

Some conditions and habits, such as haematological disorders, immunodeficiencies, inflammatory bowel diseases, vitamin deficiencies, stress, oral trauma or sensitivity to certain food have been identified as contributing factors, although the condition is often idiopathic [2].

Oral symptoms of RAS can seriously affect quality of life, although the condition is benign. Pain and burning sensation impair major oral functions, such as speech, chewing and swallowing. Therapeutic options include treatment with topical or systemic glucocorticoids, immunosuppressants, antimicrobial or anti-inflammatory therapy. During pregnancy, exposure to some drugs may adversely affect the fetus so the objective of this article is to discuss available therapeutic options for RAS in pregnancy.

Results and Discussion

PubMed database was searched for full-text articles in English language, with key words “recurrent aphthous ulcerations” and “recurrent aphthous stomatitis treatment” and “recurrent aphthous stomatitis in pregnancy”. For some agents, data for topical use in humans are limited so pregnancy recommendations are given only for systemic intake. Pregnancy risk categories have been determined by Food and Drug Administration and they represent differences in the degrees of a fetal risk regarding use of a specific drug during pregnancy (Table 1) [3].

Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, <i>or</i> animal studies demonstrate a risk and AWC studies in pregnant women have not been done during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, <i>and</i> the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. <i>Or</i> animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, <i>but</i> the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (e.g., if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities <i>or</i> there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, <i>and</i> the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (e.g. safer drugs or other forms of therapy are available).

Table 1: Pregnancy risk drug categories (FDA) [3].

Topical treatment

Treatment objectives include pain management and faster healing. Topical therapy is preferred one because of the fewer adverse effects.

Antimicrobials

Local antiseptic or antimicrobial agents in different application forms (mouthwashes, sprays, toothpastes, lozenges) can be applied to decrease duration of the lesions and microbial suprainfection and are usually applied three times a day [2]. The pregnancy risk factor for 0.2% chlorhexidine is category B. Local side-effects after rinsing with chlorhexidine several times a day during several days, include bitter taste and brown staining of the teeth and oral mucosa.

Triclosan is a wide spectrum antimicrobial agent which can be used locally three times a day in the treatment of RAS [4]. The literature data frequently correlate triclosan exposure with the development of allergies and asthma in children [5,6]. Triclosan exposure during pregnancy has not been associated with elevated concentrations of three immune system biomarkers: immunoglobulin E (IgE), thymic stromal lymphopoietin (TSLP), and interleukin-33 (IL-33). Concentration of each biomarker was positively associated with triclosan concentrations, but the association did not reach significant correlation [7]. Data regarding maternal-fetal triclosan exposure showed a poor correlation between maternal urinary and cord blood plasma triclosan concentrations [8]. Our recommendation would be to avoid the application of triclosan in pregnancy (pregnancy risk category D), until further clinical results.

Topical antibiotics such as tetracyclines and their derivatives (doxycycline and minocycline) are wide-spread antibiotics which can be used for topical therapy of RAS as a mouthwash or a gel. They inhibit local metalloproteinases that contribute to the inflammatory response and ulcer formation [9]. Systemic application of tetracyclines and their derivatives in pregnancy is characterized as pregnancy risk category D because of documented effect on fetal growth and teeth development. Evidence from the current literature show that doxycycline should be excluded from this categorization because its use in pregnancy and early childhood has not been followed by teeth staining, hepatotoxicity [10] or human teratogenicity [11].

Topical glucocorticoids

Potent (triamcinolone acetonide 0.05% - 0.5%) or superpotent corticosteroids (fluocinolone acetonide 0.025 - 0.05%, clobetasol propionate 0.05%), can be applied compounded with mucoadhesive adherents or as steroid rinses, to be applied 3 - 10 times a day [1,4]. Dexamethasone has also been shown effective for therapy of RAS [12,13]. Long-term use of local steroids may predispose to local candidal infection [14]. When steroids are topically applied, systemic absorption is poor [12] and at therapeutic doses does not represent a major teratogenic risk in humans. The risk factor of these agents used in second and third trimester of pregnancy is risk category C, and their use in first trimester of pregnancy is considered as risk category D.

Local anaesthetics

Different local anaesthetics, such as lidocaine 2%, benzocaine or tetracaine in forms of gel, spray, mouthwash or lozenges can be used for relieving symptoms during RAS [2]. Data about topical use of these agents in pregnancy are limited. Lidocaine can pass the placental barrier so the drug recommendation for therapeutic lidocaine injections in pregnancy is category D. Data from the literature have shown that the use of 1.8 mL of lidocaine 2% in combination with epinephrine was safe and efficient in restorative dental procedures during pregnancy [15].

Anti-inflammatory agents

Sucralfate: Sucralfate is a drug which was developed for treatment of gastrointestinal ulcers. It acts by providing a protective barrier on the surface of the ulcers. A few studies have shown its efficacy in decreasing the symptoms and duration of oral ulcers [2,16]. A study which compared the use of sucralfate and chlorhexidine for RAS has shown that sucralfate was significantly more effective in relieving symptoms and accelerated lesion healing [17]. Its use in pregnancy is categorized as D category.

Prostaglandin E2 (PGE2): PGE2 is a salivary constituent which has cytoprotective effect and whose concentration in saliva significantly decreases during the active stage of ulcerations [18]. Topical use of PGE2 gel (0.3 mg) twice daily for 10 days was effective in preventing the appearance of new lesions, although PGE2 was not effective in relieving symptoms and accelerating healing of the lesions [19]. Its use in pregnancy is category D, after 36th week of pregnancy, and category X until 36th week of pregnancy.

Hyaluronic acid: Hyaluronic acid is a component of extracellular matrix which has anti-inflammatory and anti-oedematous effects. Hyaluronic acid gel (0.2%) was effective and safe for the treatment of ulcerations caused by RAS and Behcet's disease [20]. Hyaluronic acid is safe for administration in pregnancy (pregnancy category risk A).

Systemic treatment

RAS usually respond well upon local therapy, but in severe cases systemic therapy may be indicated. The most effective treatments include corticosteroids and immunosuppressants.

Glucocorticoids

The drug of choice for systemic treating of RAS is prednisone. Literature suggests different regimens for prednisone. Earlier therapeutic recommendation for oral prednisone start dose was 0.5 mg/kg/day [21] or 1 mg/kg/day [22], taken as a single morning dose, which should be tapered after 1 to 2 weeks. Newer recommendation is 25 mg/day as a start dose which should be tapered after two weeks and gradually decreased until full exclusion after two months of therapy [23]. This type of treatment can be combined with above mentioned topical therapeutic options. The risk factor for prednisone in pregnancy is category C when used in second and third trimester and category D when used in first trimester.

Immunosuppressants

Colchicine

Colchicine decreases the phagocytic function of the neutrophils and is used for treatment of RAS [24]. Colchicine is prohibited in pregnancy (category X). After cessation of colchicine therapy, contraception during next three months is recommended for women and 6 months for men.

Dapsone

Dapsone acts as antibiotic and anti-inflammatory agent which inhibits neutrophil chemotactic activity and can be used for treatment of oral ulcerations [21]. The pregnancy risk factor is category D.

Thalidomide

Thalidomide is an immunosuppressant which can be used for therapy of major aphtae. Many side effects and documented teratogenicity categorizes this drug during pregnancy in category X.

Levamisole

Levamisole is another immune modulator which can be prescribed for systemic therapy of RAS in a dose of 150 mg three times a week for three consecutive weeks. Side-effects include nausea, hyperosmia, dysgeusia and agranulocytosis [25]. It is classified as pregnancy risk category C.

Pentoxifylline

Pentoxifylline is a TNF- α inhibitor which is effective in treating RAS in a dose of 400 mg three times a day, for 60 days, but does not affect the recurrence of the lesions [21,26]. Side-effects include arrhythmia. The medication is designated as pregnancy risk category C.

Clofazimine

Clofazimine is a drug developed to treat Mycobacterium tuberculosis. It has shown to be effective for treatment of RAS in a dose of 100 mg a day, during the 30 days, and for prophylaxis of RAS when taken for 6 months, a 100 mg every other day [27]. It is classified as pregnancy risk category C.

Infliximab

Infliximab is a monoclonal antibody which blocks TNF for the treatment of refractory and recurrent oral and genital ulcers. The recommended dose is 5 mg/kg body weight infusion at 0, 2, and 6 weeks [28]. Side-effects include potential reactivation of infections, immune-suppression, worsening of nervous symptom disorders, bleeding tendency, liver problems, heart attack and allergic reactions. It is classified as pregnancy risk category D.

Etanercept

Etanercept is a fusion protein of 75-kDa TNF- α receptor and the Fc portion of human IgG1. When injected subcutaneously twice weekly, it has been effective for oral, but not for genital ulcerations [2,29]. Serious side-effects categorize this drug as pregnancy risk category D.

Cyclosporine A

Cyclosporine A is an immunosuppressive agent that interferes with B- and T-cell activation [30] and can be used as monotherapy or in combination with systemic corticosteroids for the treatment of RAS. Topical application of bioadhesive gel containing cyclosporine A has also shown promising results for the treatment of RAS [31]. It is designated as pregnancy category X.

Azathioprine and methotrexate

Azathioprine and methotrexate are anti-metabolites which have also been used for systemic treatment of RAS, as monotherapy or in combination with other drugs [2]. Their administration can affect complete blood count and liver function and they are both contraindicated in pregnancy (pregnancy risk category X).

Preventive treatment?

Current therapeutic options mostly do not affect the frequency of the formation of new ulcers. Results from a study involving a small number of patients reported that topical use of prostaglandin E2 (0.3 mg) reduced the appearance of new ulcerations [19]. Two reports from the literature pointed out that vitamin B12, in a sublingual dose [32] or within adhering discs [33] is effective in prevention of new ulcerations, regardless of the serum vitamin B12 level. Zinc sulphate in a dose of 150 mg a day has shown prophylactic action on recurrence of RAS [34]. Clofazimine has also shown to have a preventive effect on formation of new ulcerations, however, in a study with small number of patients [27]. Evidence from recent literature show that avoiding of dentifrices containing sodium-lauryl-sulphate significantly reduces symptoms and recurrence of oral ulcerations [35]. Therefore, patients with RAS should be advised about these options.

Conclusion

Pregnant patients with RAS should be informed about the risk level of the potential drug for the fetus so that they can actively participate in the decision about the treatment. Topical therapy is the therapy of choice. It is effective in most cases and has well-tolerable side-effects. Systemic therapy should be considered for patients resistant to local therapy, taking into account possible fetal side-effects and pregnancy risk category. Until the aetiology of RAS is clarified, the treatment remains palliative.

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Conflict of Interest

No conflict of interest.

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