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REVIEW ARTICLE

Medical treatments for pregnant patients with oral lichen planus

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ABSTRACT

Oral lichen planus (OLP) is a common chronic inflammatory disorder that manifests as papular, reticular, or erosive lesions. OLP seriously affects a patient's quality of life, as it is associated with symptoms such as pain and a burning sensation. It is also accompanied by a risk of carcinogenic tendency. During pregnancy, the treatment will be more complicated because of the effect of medical treatment on both the mother and foetus. Thus, appropriate drugs for those pregnant patients will be more essential. This study aimed to review the safety of drugs used for the treatment of OLP during pregnancy and to establish an appropriate treatment plan for pregnant patients with OLP.

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Introduction

Oral lichen planus (OLP) is a T cell-mediated chronic inflammatory mucocutaneous disease of unknown etiology, which is estimated to affect 0.5–2.0% of the general population. OLP can affect any part of the oral cavity; however, it mostly affects the buccal mucosa, tongue, labial mucosa and gingival.[1] It can present as papular, reticular, or plaque-like lesions that can be atrophic, erosive-ulcerative, or bullous. It seriously affects the quality of life, as symptoms of pain and a burning sensation, as well as a risk of carcinogenic tendency.[2]

During pregnancy, changes in the mother's hormonal levels and the effects of medical therapy on both mother and foetus generally make disease treatment complicated. It is generally accepted that the foetus may be adversely affected by the mother's exposure to drugs. As a result, pregnant patients with OLP should be treated prudently, particularly if the treatment presents any risks to the mother or the foetus. The objectives of this article are to discuss the safety of medicines used for the treatment of OLP during pregnancy and to establish an appropriate treatment plan for pregnant patients.

The US Food and Drug Administration (FDA) has assigned a risk factor category (A, B, C, D and X) (Table 1) to each drug to evaluate its safety based on the level of risk it poses to a foetus.[3] However, the risk factors were oversimplified; therefore, the newest edition of *Drugs in Pregnancy and Lactation* [4] suggests the use of the definitions of pregnancy recommendations instead of the risk factors. The pregnancy recommendations contain 17 categories: Compatible, No (limited) human data-probably compatible, Compatible – maternal ≫ embryo-foetal risk, Human data suggest low risk, No (limited) human data – animal data suggest low risk, No (limited) human data – animal data suggest moderate risk, No (limited) human data – animal data suggest risk, No (limited) human data - animal data suggest high risk, Contraindicated – 1st trimester, Contraindicated – 2nd and 3rd trimesters, Contraindicated, No (limited) human data – no relevant animal data, Human data suggest risk in 1st trimester, Human data suggest risk in 1st and 3rd trimesters, Human data suggest risk in 2nd and 3rd trimesters, Human data suggest risk in 3rd trimester, and Human (and animal) data suggest risk.[4] The above pregnancy recommendations are intended to assist in the clear determination of the level of risk of a special drug (Appendix Table).

Topical agents

Owing to their fewer adverse effects, topical agents are preferred for relieving symptoms and accelerating wound healing during the management of OLP.

Glucocorticoids

Topical glucocorticoids are the mainstay of the palliative treatment of OLP. They are used to reduce the associated inflammation and pain. It has been reported that topical corticosteroids such as betamethasone, fluocinolone, and triamcinolone are effective in most patients.[5–7] The risk factor of these agents are category C, and category D used in 1st trimester. Although they can cross the placenta and reach the foetus, their systemic absorption is relatively poor. In addition, current studies have shown that they do not represent a major teratogenic risk in humans when they administered at therapeutic doses.[8,9] The pregnancy recommendation of

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Table 1. Risk factors of FDA.

Category	Definitions
A	Controlled studies in women fail to demonstrate a risk to the foetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of foetal harm appears remote.
B	Either animal-reproduction studies have not demonstrate a foetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimester).
C	Either studies in animals have revealed adverse effects on the foetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drug should be given only if the potential benefit justifies the potential risk to the foetus.
D	There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated foetal abnormalities or there is evidence of foetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicate in women who are or may become pregnant.

betamethasone indicates that its potential benefit to the mother far outweighs its known or unknown risks to the foetus (Compatible – maternal benefit ≫ embryo-foetal risk). The pregnancy recommendation of topical triamcinolone is 'Compatible', whereas that of topical fluocinolone is based on limited human data; however, animal data suggest risk.

Immunosuppressants

Even though topical corticosteroids are the first choice treatment for OLP, some patients are refractory to them. For this reason, more potent immunosuppressants or immunomodulatory agents, such as cyclosporine,[10] tacrolimus,[11] pimecrolimus,[12] and tretinoin [13] could be used in place of topical corticosteroids. The pregnancy risk category of the above mentioned agents is C. The pregnancy recommendation of cyclosporine is based on limited human data; however, animal data suggest low risk, whereas that of pimecrolimus is not based on human data (No human data – animal data suggest low risk).The pregnancy recommendations of both topical tacrolimus and tretinoin (Human data suggest low risk) indicate that because of limited human pregnancy experiences, the drugs do not present significant risks to the foetus. Moreover, some experts have suggested that tretinoin should be contraindicated in pregnancy.[14] It should be noted that the pregnancy risk categories and pregnancy recommendations were developed based on systemic administration of the above drugs. Therefore, because of limited human data on the topical use of the drugs, further research is required on their safety following topical administration.

Antimicrobials

Chlorhexidine, povidone-iodine, and nystatin are commonly used as topical antiseptics on erosive lesions in patients with OLP to control infection of the lesions. The pregnancy risk classifications of chlorhexidine and nystatin are categories B and C, respectively. Gerald et al. [4] have suggested that chlorhexidine and nystatin can be used during pregnancy (compatible). Iodide can affect the development of the foetal thyroid gland; therefore, since iodide can cross the placenta and reach the foetus easily, the pregnancy risk category of povidone-iodine is D. In addition, the pregnancy recommendation of povidone-iodine (Human data suggest risk in 2nd and 3rd trimesters) suggests that the complex may be a risk to the foetus in the 2nd and 3rd trimesters but not in the 1st trimester.[15] Moreover, the American Academy of Paediatrics has specified that the use of iodides as expectorants during pregnancy is contraindicated.[16]

Systemic agents

Treatment of OLP with systemic agents may be required if the lesions are widespread or if there is a coexisting disease that is difficult to treat. The systemic treatment mainly involves the use glucocorticoids, immunosuppressants, immunomodulators and/or vitamins.

Glucocorticoids

Prednisone is a synthetic glucocorticoid that suppresses the hypothalamic-pituitary-adrenal (HPA) axis activity of a patient. However, long-term prednisone use carries the risk of adverse effects including depression, hyperglycemia, lipodystrophy, a moon face, and further HPA axis suppression.[17] In the treatment of OLP in which the patient has a wide range of erosive lesions, prednisone can be administered at a low dose and for a short duration. Furthermore, prednisone can be successfully used to prevent neonatal respiratory distress syndrome when premature delivery occurs between 28 and 35 weeks of gestation.[18] Although no abnormal outcomes were observed in most studies that reported the use of prednisone during gestation, a prospective cohort study showed that prednisone increases the risk of orofacial clefts.[20] Moreover, the risk classification of prednisone is category C; however, category D is used in the 1st trimester. The pregnancy recommendation of prednisone indicates that human data suggest that there may be a risk for developmental toxicity throughout pregnancy; however, the risk may be acceptable if the maternal condition requires treatment with the drug. Furthermore, a recent study suggested that treatment with corticosteroids at low dosages is safe during the 2nd and 3rd trimesters if the patient is mildly ill.[21] In summary, prednisone poses a small risk to a developing foetus. Although the available evidences support that prednisone could be administered to control some maternal diseases, the mother should be informed of the associated risks so that she can actively participate in the decision on whether to use the drug during her pregnancy.

Other glucocorticoids such as prednisolone, betamethasone, and hydrocortisone are also generally classified as category C drugs but as category D drugs during the 1st trimester. The pregnancy recommendations of prednisolone and hydrocortisone are the same as that of prednisone, whereas betamethasone is considered as 'Compatible'.

Immunosuppressants

Thalidomide

Thalidomide can be used to treat severe erosive lesions in OLP when glucocorticoid therapy is ineffective or contraindicated.[22] However, it has a long and well-known history. It was approved in 1957 for the treatment of nausea during early gestation but was banned in the early 1960's after approximately 10,000 babies were born with phocomelia.[23] In addition, the teratogenic effects of thalidomide in mice, rats, rabbits, monkeys, and humans have been extensively studied and documented.[24] What's more, thalidomide was one of the first group of drugs that were clearly shown to be human teratogens and was categorized as a pregnancy risk factor X drug. The pregnancy recommendation of thalidomide is that it is 'Contraindicated' at any time during pregnancy.

Tacrolimus

Tacrolimus is a macrolide immunosuppressant agent mostly used for preventing rejection of transplanted organs. Recently, it has been shown to be effective in the management of recalcitrant erosive OLP with the powerful immunosuppressive activities by inhibiting T-cell production of proinflammatory cytokines.[11,25] The use of tacrolimus during human pregnancy is not associated with teratogenicity; however, it has been reported that tacrolimus has abortifacient properties in three animal species.[26,27] In addition, its pregnancy risk factor category is C and its pregnancy recommendation (Human data suggest low risk) indicates that its use in human pregnancy does not present a significant risk to the foetus.

Hydroxychloroquine

Hydroxychloroquine is a type of anti-malarial drugs and an immunologic that is used in improving OLP with decreasing the up-regulated frequencies of Tregs.[28] As there is limited human data on the use of hydroxychloroquine, it appears that it does not pose a significant risk to an embryo/foetus, especially if it is used at low doses. Some investigators have reported similar conclusions from studies on the safety of hydroxychloroquine in the treatment of systemic lupus erythematosus.[29,30] Hydroxychloroquinehas been classified as a pregnancy risk factor C drug based on limited human pregnancy experiences. However, the characteristics of the drug suggest that it does not present a significant risk to the foetus (Limited human data - probably compatible).

Azathioprine

Azathioprine (AZA) is a cytotoxic anti-metabolite that is used to inhibit purine synthesis; however, purine synthesis is especially important for the proliferation of leukocytes.[31] AZA has been shown to be an effective steroid-sparing treatment for generalized lichen planus.[32] It does not appear to cause anomalies in humans although it is teratogenic in rabbits.[31] However, exposure to AZA during the 3rd trimester may result in immunosuppression.[33] The pregnancy risk factor category of AZA is D; whereas its pregnancy recommendation is 'Human data suggest risk in 3rd trimester'.

Cyclosporine

Cyclosporine is used as an immunosuppressive agent to prevent the rejection of kidney, liver, or heart allografts. Moreover, it is useful for treating OLP since it inhibits CD4 T cell activity.[34] It has been reported that cyclosporine is not an animal teratogen.[35,36] In addition, the limited evidence gathered from women suggests that it is unlikely to be a human teratogen. Its pregnancy recommendation is based on limited human data but animal data suggest low risk (Limited human data – animal data suggest low risk), and it belongs to pregnancy risk factor category C.

Immunomodulators

Interferon alpha and levamisole are immune-modulating agents that are effective for the treatment of OLP.[37] They are both in pregnancy risk factor category C and based on a limited number of human cases, they do not appear to pose significant risks to the foetus. The pregnancy recommendation of levamisole is not reported; however, that of interferon alpha (Limited human data – probably compatible) is based on limited human pregnancy experiences although its characteristics suggest that it does not represent a significant risk to the foetus.

Vitamins

Tretinoin

Tretinoin is a retinoid metabolite of naturally occurring vitamin A. It has the ability to modify abnormal follicular keratinization and modulate the proliferation and differentiation of epidermal cells. Tretinoin is a valuable treatment for lichen planus if it is administered at a low dose to patients who fail to respond to other therapies.[38] Like other retinoids, tretinoin is a potent teratogen when it is administered systemically during early gestation. It produces a pattern of birth defects termed retinoic acid embryopathy; therefore, it is contraindicated during the 1st trimester of pregnancy. The pregnancy risk factor category of tretinoin is D.

Beta-carotene

Beta-carotene is a natural precursor of vitamin A. It exhibits strong antioxidant and immune-regulating properties but no toxicity.[39,40] Studies in animals have not shown a teratogenic effect of beta-carotene.[41] In addition, there is no known embryo-foetal risk associated with its use in pregnancy. Its pregnancy recommendation is 'Compatible' and its pregnancy risk factor category is C.

Table 2. Pregnancy recommendations of common medicine for the treatment of OLP.

Common medicine	Risk factor	Pregnancy recommendation
Betamethasone	C (D used in 1st trimester)	Compatible—maternal ≫ embryo-foetal risk
Fluocinolone (Topical)	C (D used in 1st trimester)	Limited human data—animal data suggest risk
Triamcinolone (Topical)	C (D used in 1st trimester)	Compatible
Cyclosporine	C	Limited human data—animal data suggest low risk
Tacrolimus	C	Human data suggest low risk
Pimecrolimus	C	No human data—animal data suggest low risk
Tretinoin (Topical)	C	Human data suggest low risk
Chlorhexidine	B	Compatible
Nystatin	C	Compatible
Povidone-iodine	D	Human data suggest risk in 2nd and 3rd trimesters
Prednisone	C (D used in 1st trimester)	Human data suggest risk
Prednisolone	C (D used in 1st trimester)	Human data suggest risk
Hydrocortisone	C (D used in 1st trimester)	Human data suggest risk
Thalidomide	X	Contraindicated
Tacrolimus	C	Human data suggests low risk
Hydroxychloroquine	C	Limited human data—probably compatible
Azathioprine	D	Human data suggest risk in 3rd trimester
Cyclosporine	C	Limited human data—animal data suggest low risk
Interferon alpha	C	Limited human data—probably compatible
Levamisole	C	Not mentioned
Tretinoin (System)	D	Contraindicated in 1st trimester
Beta-carotene	C	Compatible
Vitamin E	C	Compatible

Vitamin E

Vitamin E (VE) comprises a group of fat-soluble vitamins that are essential for human health. As an antioxidant, VE plays a preventive role in potentially-malignant disorders including oral lichen planus, leukoplakia and erythroplakia.[19] It is a pregnancy risk factor A drug; however, it is considered as a category C drug if it used at doses above the recommended dietary allowance. Neither a deficiency nor an excess of VE has been known to be associated with maternal or foetal complications during pregnancy. Its pregnancy recommendation is 'Compatible'.

Conclusion

In conclusion, medical treatment is unnecessary for asymptomatic reticular lesions of OLP but necessary for the symptomatic or erosive types (Table 2). It is important that pregnant patients avoid taking medicines as much as possible. However, when necessary, they have to accept medical treatment only after consultation with their physicians. Furthermore, pregnant patients must be informed of the risk of every drug they take so that they can actively participate in the decision on whether to use a drug or not. However, due to the limited human data on drugs administered during pregnancy, medical treatment during pregnancy is still improving. Moreover, most of the effective agents for OLP should be used cautiously during pregnancy until more data are available to assess their risks to the foetus. In addition, obstetricians, pharmacists, and oral medicine specialists must work together to ensure the efficacy and safety of each treatment administered to pregnant women as well as the potential risks of the treatment to the foetus.

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Appendix

Table. Definitions of pregnancy recommendations.

Category	Definitions
Compatible	The human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, is adequate to demonstrate that the embryo-foetal risk is very low or non-existent. Animal reproduction data are not relevant.
No (limited) human data–probably compatible	There may or may not be human pregnancy experience, but the characteristics of the drug suggest that it does not represent a significant risk to the embryo-foetus. For example, other drugs in the same class or with similar mechanisms are compatible or the drug does not obtain significant systemic concentrations. Any animal reproduction data are not relevant.
Compatible–maternal $\gg$ embryo-foetal risk	There may or may not be human pregnancy experience, but the potential maternal benefit far outweighs the known or unknown embryo-foetal risk. Animal reproduction data are not relevant.
Human data suggest low risk	There is limited human pregnancy experience, either for the drug itself or drugs in the same class or with similar mechanisms of action, including the 1st trimester, suggesting that the drug does not represent a significant risk of developmental toxicity at any time in pregnancy. The limited human pregnancy data outweigh any animal reproduction data.
No (limited) human data–animal data suggest low risk	Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity. The drug does not cause developmental toxicity in all animal species studies at doses $\leq$10 times the human dose based on body surface area.
No (limited) human data–animal data suggest moderate risk	Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity. The drug causes developmental toxicity in one animal species at doses $\leq$10 times the human dose based on body surface area.

(*continued*)

Table. Continued

Category	Definitions
No (limited) human data–animal data suggest risk	Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity. The drug causes developmental toxicity in two animal species at doses $\leq$10 times the human dose based on body surface area.
No (limited) human data–animal data suggest high risk	Either there is no human pregnancy experience or the few pregnancy exposures have not been associated with developmental toxicity. The drug causes developmental toxicity in there or more animal species at doses $\leq$10 times the human dose based on body surface area.
Contraindicated–1st trimester	Human exposures in the 1st trimester, either to the drug itself or drugs in the same class or with similar mechanisms of action, have been associated with developmental toxicity. The drug should not be used in the 1st trimester.
Contraindicated–2nd and 3rd trimesters	Human exposures in the 2nd and 3rd trimesters, either to the drug itself or drugs in the same class or with similar mechanisms of action, have been associated with developmental toxicity. The drug should not be used in the 2nd and 3rd trimesters.
Contraindicated	Human exposures at any time in pregnancy, either to the drug itself or drugs in the same class or with similar mechanisms of action, have been associated with developmental toxicity. Animal reproduction data, if available, confirm the risk. The drug should not be used in pregnancy.
No (limited) human data–no relevant animal data	There is no human pregnancy data or relevant data in animals, or the human pregnancy experience, that may or may not include the 1st trimester, is limited. The risk in pregnancy cannot be assessed.
Human data suggest risk in 1st trimester	Evidence suggests that there may be an embryo-foetal risk for developmental toxicity in the 1st trimester but not in the 2nd and 3rd trimesters. The human pregnancy data outweigh any animal reproduction data.
Human data suggest risk in 1st and 3rd trimesters	Evidence suggests that there may be an embryo-foetal risk for developmental toxicity in the 1st and 3rd trimesters but not in the 2nd trimester. The human pregnancy data outweigh any animal reproduction data.
Human data suggest risk in 2nd and 3rd trimesters	Evidence suggests that there may be a foetal risk for developmental toxicity in the 2nd and 3rd trimesters but not in the 1st trimester. The human pregnancy data outweigh any animal reproduction data.
Human data suggest risk in 3rd trimester	Evidence suggests that there may be a foetal risk for developmental toxicity in the 3rd trimester, or close to delivery but not in the 1st and 2nd trimesters. The human pregnancy data outweigh any animal reproduction data.
Human (and animal) data suggest risk	The human data for the drug or drugs in the same class or with the same mechanisms of action, and animal reproduction data if available, suggest there may be a risk for developmental toxicity throughout pregnancy. Usually, pregnancy exposure should be avoided, but the risk may be acceptable if the maternal condition requires the drug.