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INVITED ARTICLE

Treatment of dermatologic connective tissue disease and autoimmune blistering disorders in pregnancy

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ABSTRACT: Autoimmune skin disease occurs in pregnancy, and treatment is often required to control both maternal disease and fetal outcomes. Here we present the available safety data in pregnancy and lactation for medications used to treat autoimmune skin diseases, including cutaneous lupus erythematosus, dermatomyositis, morphea and systemic sclerosis, pemphigus vulgaris, pemphigus foliaceus, and pemphigoid gestationis. A PubMed search of the English-language literature using keywords, "pregnancy" "rheumatic disease," and "connective tissue disease" was performed. Relevant articles found in the search and references were included. Reasonable evidence supports the careful and cautious use of topical steroids, topical calcineurin inhibitors, systemic corticosteroids, hydroxychloroquine, and azathioprine in pregnancy. Case reports or clinical experience suggest intravenous immunoglobulin, dapsone, phototherapy, rituximab, and plasmapheresis may be safe. Several treatment options exist for autoimmune skin disease in pregnancy and lactation, and should be considered when treating these patients.

KEYWORDS: autoimmune skin disease, blistering disease, blistering disorders, cutaneous lupus erythematosus, dermatomyositis, lactation, morphea, pemphigoid gestationis, pemphigus foliaceus, pemphigus vulgaris, pregnancy, rheumatic skin disease

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Introduction

Autoimmune skin disease, including connective tissue diseases and autoimmune blistering diseases, occur in young women who are either pregnant or of childbearing potential and present challenges to treatment (1). Choice of therapy

has important implications for counseling on contraception, planned conception, and disease control. Preconception counseling is felt to improve pregnancy outcomes, highlighting the need to consider these issues initially and to frequently revisit them with any affected young woman (2,3).

The choice of medication is largely based on safety, but also on disease activity and tolerability of the medication in the patient. The risks may be well-known or uncertain and need to be weighed against the risk that these diseases can pose for the patient, including the risk of disease flare during pregnancy and lactation. These challenges are compounded by the lack of evidence-based studies in this field. Clinical trials in pregnant women are considered unethical in many circumstances, so data are often extrapolated from other diseases (i.e., organ transplantation, malaria, inflammatory bowel disease (IBD)), animal models, case reports or series, and retrospective population-based studies.

The measures of success are control of the mother's disease and fetal health measures, including fetal survival, fetal growth restriction, gestational weight, and congenital abnormality. Maternal health complications including gestational diabetes, preeclampsia and eclampsia also have serious implications for fetal health. Neonatal passage of the disease, for example with neonatal pemphigus vulgaris and neonatal lupus, is also a consideration when choosing therapy.

Communication with the patient's obstetrician is critical. No medication is felt to carry no risk to the mother or fetus; however, some are considered safer than others. The US Food and Drug Administration (FDA) pregnancy safety classification system is based on data from the medication's first market application. There is no mandate to update the classification with the results of human experience limiting their clinical utility (4,5).

Here we will summarize the data available for the safety and efficacy in pregnancy and lactation of the main immunomodulatory and immunosuppressive agents used to treat autoimmune cutaneous conditions. Where available, evidence for the management in men in the preconception period is included. This is followed by recommendations for treatment of cutaneous lupus erythematosus, dermatomyositis, morphea, pemphigus vulgaris, pemphigus foliaceus, and pemphigoid gestationis in pregnancy.

Disclaimer

This is an evolving field with limited data available. Reference to the most recent literature is warranted in the setting of patient care. Please note there may be circumstances where these guidelines are not clinically applicable and it may be necessary to depart from them.

Topical corticosteroids

Topical steroids are the first-line skin-directed therapy for many autoimmune skin diseases. They are classified as FDA pregnancy class C. While animal data show a partially dose-dependent teratogenic effect, there is substantial data from the human experience supporting their safety, although some risks have been noted. A large Hungarian population-based case control study showed no increase in congenital abnormalities in babies exposed to topical steroids in utero (6). A Danish population-based study showed no increased risk of malformations or preterm delivery in babies exposed to topical steroid during pregnancy, although there was a trend for a dose–response relationship with low birthweight (7). A large retrospective case control study looking at many forms of corticosteroid use found no association of topical corticosteroids with orofacial clefting, a specific and relatively common congenital abnormality that has been loosely associated with cortiocosteroid use (8).

Two large population-based cohort studies were performed that ascertained exposure based on prescriptions registry data. One study, from the United Kingdom based on 84 000 pregnant women, showed a significant association of fetal growth restriction with maternal prescriptions for potent or very potent topical corticosteroids, but not with mild to moderate topical corticosteroids. The number needed to harm was 168 (9). A Danish population-based study found an increased risk of orofacial clefting with topical steroids, but not with other forms of corticosteroids. However, when dose and potency response relationship was examined, no causal association could be made (10).

The risk of orofacial clefts, fetal growth restriction and fetal hypothalamus–adrenal–axis suppression are better understood in the setting of systemic corticosteroids and will be discussed further in that section. Theoretically, topical steroids pose a significantly decreased risk because of the small amount of systemic absorption when used in a steroid-sparing fashion relative to systemic agents.

Chi et al. published a Cochrane review in 2009 (11) and then subsequently developed evidence-based guidelines for the use of topical steroids in pregnancy (12) and other groups have made identical recommendations (13). Recommendations include using mild or moderate topical corticosteroids in preference to more potent topical corticosteroids in pregnancy. Potent topical steroids should be used as second-line therapy, for short durations and appropriate obstetric care should be sought because of a potential increased risk of fetal growth restriction. Areas of thin skin, such as the genitals, eyelids and flexures are thought to have higher rates of absorption and some recommend to not treat those areas with topical steroids during pregnancy.

Topical steroids can be applied safely in lactation. When applying to the nipple of a breast-feding mother, low to mid potency steroids should be used. Avoid class 1 corticosteroids on the skin of the nipple. Instruct the mother to apply directly after feeding so that the medication has opportunity to be absorbed into the skin (14).

Topical calcineurin inhibitors

Topical calcineurin inhibitors, classified as FDA pregnancy class C, have limited efficacy in severe autoimmune skin diseases, but may be considered as steroid-sparing agents if prolonged use of topical steroids is needed or if use on the face is required. There are limited data on the use of topical calcineurin inhibitors in pregnancy, but safety can be extrapolated from the transplant literature. Lam et al. summarize the available data and note that low birthweight and preterm delivery are seen in pregnant women on systemic tacrolimus. Several infants were born with hyperkalemia. Data show systemic absorption of tacrolimus after topical administration is low, although they are increased in the setting of defective dermal barrier function, raising caution in the use of these agents in atrophic or ulcerated lesions (15).

Topical calcineurin inhibitors are thought to be safe in lactation although studies are lacking. These agents should not be applied directly to the nipple in a breast-feeding mother (14).

Oral steroids

Systemic steroids have a greater bioavailability than topical steroids and thus the risks in pregnancy are greater. Nonetheless, systemic corticosteroids are an important and safe therapeutic option in pregnancy. There is variability in placental metabolism and transplacental passage of different systemic corticosteroids (16). Non-fluorinated corticosteroids, like prednisone, are almost completely inactivated by placental 11-beta hydroxysteroid dehydrogenase, preventing passage to the developing embryo or fetus. The fluorinated compounds, such as dexamethasone and betamethasone, pass through the placenta to the fetus, and are used to promote fetal lung maturity in preterm labor (4,16). Because prednisone will not pass through the placenta as easily, it is the preferred choice of systemic cortisone during pregnancy. Prednisilone, the active metabolite of prednisone, is classified as FDA category C; the brand Flo-Pred™ (Taro Pharmaceuticals, Hawthorne, NY, USA) is classified as FDA category D.

Studies have shown that prenatal exposure to prednisone may result in intrauterine growth retardation, premature rupture of membranes, or preterm delivery (16). Small studies have demonstrated an increased risk of orofacial clefts starting 4 weeks before conception through 12 weeks after conception (8). Larger population-based studies have shown no increase in the risk of orofacial clefts or other congenital anomalies (10). Lip formation is completed during weeks 5–7 after conception, and palate formation is completed 8–12 weeks after conception. The risk of cleft lip or palate with administration of corticosteroids before the time of lip and palate development suggests that the effects of the corticosteroids may extend beyond their period of intake. Another possible effect is fetal hypothalamus–pituitary–adrenal (HPA) axis suppression. Although corticosteroids used in maternal disease are typically ones that are metabolized by the placental enzyme, receptor saturation can occur and cases of fetal adrenal suppression have been documented (17). A systematic review showed evidence of a blunted fetal HPA function with respect to pain-related stress in exposed neonates and noted that the HPA axis usually recovers within the first 2 weeks postpartum, but depression may persist for 4 months. HPA axis suppression appears to be dose-related and the long-term sequelae are not well understood (18).

When systemic corticosteroids are required, many recommend prolonged use of no more than 7.5 mg/day of prednisone and every effort should be made to avoid doses greater than 20 mg daily. Use of the lowest effective dose of corticosteroids possible is recommended along with counseling regarding the low risk of oral clefts with first-trimester exposure. Calcium and vitamin D

supplementation is recommended in light of the deleterious effects of corticosteroids on bone metabolism (2). Stress doses of steroids may be required in the event of pregnancy complications (19). Finally, gestational diabetes, hypertension, preeclampsia, and eclampsia are pregnancy-specific morbidities that can be directly exacerbated because of corticosteroids, and these risks should be taken into account.

Prednisolone transmission in breast milk is less than 0.1% of the dose ingested by the mother, which is usually less than 10% of the infant's endogenous cortisol production. Peak levels of steroids in breast milk occur 2 hours after a dose and decline rapidly, so nursing 3–4 hours after a dose is recommended (4,19,20).

Antimalarials

Hydroxychloroquine (HCQ) is an antimalarial agent with immunomodulating activity that has proven efficacious in the setting of many autoimmune skin diseases. Other antimalarials, including chloroquine and quinine, have immunomodulatory activity; however, HCQ has the strongest safety record for the treatment of dermatologic conditions in pregnancy. HCQ is classified as FDA pregnancy category C.

Much of the available safety data for these agents comes from the malaria prophylaxis literature (21). There is one limited randomized control trial of HCQ in pregnancy that included 20 consecutive patients with systemic lupus erythematosus (SLE) or discoid lupus erythematosus, many of whom were also on prednisone at the time. No congenital abnormalities were noted, and no neurologic or ophthalmologic abnormalities were seen in follow-up. Additionally, this study showed that HCQ use in pregnancy led to a decrease in disease activity and prednisone dose (22). A prospective study compared three groups of pregnant women with SLE, one group without exposure to HCQ, one with continued use of HCQ, and the third group with cessation of HCQ 3 months prior to conception. No statistical difference in negative fetal events, such as miscarriage, stillbirth or congenital abnormalities, was found between the groups. There was a higher degree of lupus activity in the group that stopped HCQ therapy, while those who were continued on HCQ were able to lower their prednisone dose (23). Ruiz-Irastorza et al. reported on greater than 300 pregnant women with SLE or malaria treated with antimalarials without any unexpected malformation or cases of ocular, auditory, or neurological toxicity (24). A recent meta-analysis from 2009 concluded that HCQ is not associated with any increased risk of congenital defects, spontaneous abortion, fetal death, or prematurity (25). Many reviews support safety of HCQ in pregnancy (26) and advocate for continued use during pregnancy (24).

There are reports of auditory toxicity and retinal deposition in animal models, although there is no evidence of fetal ocular toxicity with either chloroquine or HCQ (27,28). A large Cochrane meta-analysis supports the safety of chloroquine in the setting of malaria prophylaxis in pregnancy (29). However, the malaria prophylaxis dose is lower than the dose used in autoimmune skin disease (500 mg of chloroquine weekly in malaria prophylaxis versus 250 mg daily or <3.5 mg/kg/day in autoimmune skin disease). Also HCQ has lower placental drug concentration that chloroquine. In the setting of treatment for autoimmune skin disease HCQ is the preferred antimalarial agent (30). These authors do not recommend the use of either chloroquine or quinine in pregnancy.

Additionally, HCQ may decrease the risk of recurrent cardiac neonatal lupus and congenital heart block in mothers with SLE and anti-Ro antibodies (31). HCQ also has anti-thrombotic effects, and may protect against osteoporosis in patients taking corticosteroids, although the mechanisms of these clinical effects are not well defined (26).

Excretion of HCQ into breast milk was very low (<0.2 mg/kg/day), and the level is thought to be non-toxic (32). HCQ and chloroquine are considered safe for use in breast-feeding (20) although HCQ has been studied more rigorously and is the preferred agent (14).

Dapsone

Data on safety of dapsone is also extrapolated from malaria and leprosy literature. Dapsone is pregnancy category C. Dapsone may have clinical role in pregnant patients with pemphigus. Animal studies have shown that even at high doses, dapsone is not teratogenic. A review suggested data on the tolerability of dapsone in pregnancy is limited making meaningful risk assessment difficult (21,33). Glucose-6-phosphate dehydrogenase levels should be investigated prior to starting this medication due to the risk of anemia. Risks to the fetus include neonatal hyperbilirubinemia and hemolytic anemia. Of 924 reported cases of fetal dapsone exposure, only two congenital abnormalities were reported, and no causal link could be

established (33). There are reports of infants who developed hemolytic anemia after exposure to dapsone from breast milk. Dapsone is classified as compatible with breast-feeding (20). Infants should be monitored for signs of hemolytic anemia (14).

Azathioprine

Azathioprine is FDA pregnancy class D, reflecting a potential fetal risk that may be outweighed by the benefits of treatment. However, there is substantial data supporting its safety in pregnancy in the setting of organ transplantation, rheumatic disease and autoimmune bowel disease. Both azathioprine and its metabolites 6-mercaptopurine and 6-thiouric acid cross the placenta (4). The main risks are preterm and low-birthweight infants. Azathioprine is felt to be safe in pregnancy, but sporadic anomalies and hematologic toxicities have been reported. Initially, there were several reports of newborns with leukopenia and thrombocytopenia born to mothers on azathioprine. After initiating a protocol where the dose of azathioprine was halved at 32 weeks gestation if the mother's leukocyte count was less than 1 standard deviation below the mean, there were no reports of leukopenia or thrombocytopenia in the newborn infants (34).

No pattern of congenital malformation has emerged although there may be a slight increase risk of atrial or ventricular septal defects (35). In IBD, a systematic review showed that thiopurine exposure in women was not associated with low birthweight or congenital anomalies; however, an association with preterm birth was noted (36). The use of thiopurines by men at conception is not associated with congenital abnormalities (36,37). Obstetricians may offer patients a detailed ultrasound to confirm normal morphologic development.

Although, pregnancy can occur safely while on azathioprine, some patients on this medication will be trying to avoid pregnancy. It these patients is important to inform them that azathioprine has been reported to interfere with the effectiveness of intrauterine devices (IUDs), with reports of several patients becoming pregnant with their IUD in place (38).

No adverse events have been reported in breast-fed infants exposed to maternal azathioprine (35,39,40). A small study showed that excretion of azathioprine in breast milk occurs within 4 hours of ingestion, with only 10% excreted after 10 hours of ingestion, prompting the recommendation to breast-fed at least 4 hours after taking the medication. Breast-fed infants should be monitored for decreased growth rate and immunosuppresion (14).

Phototherapy

Phototherapy may be helpful in some forms of morphea, but is not appropriate to treat photosensitive connective tissue processes. In a review of treatments for psoriasis in pregnancy, Lam et al. noted the absence of data regarding the safety of ultraviolet B (UVB) and narrow-band UVB (NBUVB) in the setting of pregnancy, despite the shared clinical experience and notion of its safety given that the light cannot penetrate beyond the superficial skin layers to affect the developing embryo or fetus (15). Folic acid depletion, attributed to photodegradation of folate, has been reported with NBUVB therapy, although the magnitude of the effect is unclear. Some recommend checking folic acid levels in pregnant patients undergoing phototherapy and to supplement folate if needed (41).

Topical psoralen and UVA therapy is another potential option. Studies examining risk with fetal exposure to systemic psoralen were not powered sufficiently to prove safety (42). Although there are not studies of topical psoralen, authorities suggest localized use of topical oxsoralen may be safe in pregnancy due to the lack of systemic absorption in disease like psoriasis (15). Oxsoralen has not been studied during breast-feding.

Rituximab

Rituximab use is increasingly common for autoimmune blistering skin diseases. Placental passage of rituximab is minimal in the first trimester, moderate in the second, and extensive in the third, and may affect fetal B cell development. Cynomolgus monkey fetuses exposed during pregnancy had reduced B cell numbers that returned to normal 6 months after birth. Currently, women of childbearing age are advised to use contraception during treatment and 12 months thereafter because rituximab is detectable in serum for up to 6 months (43). Ton et al. found 12 reports of rituximab use in pregnancy. Some of the offspring had neonatal B cell abnormalities, but many were in the setting of rituximab coadministration with chemotherapeutic regimens. All infants showed B cell recovery without infectious complications. The lack of

serious infectious complications in the infant may be due to protection from maternal immunoglobulins. Also, neonatal immunoglobulin production continued as indicated by normal response to vaccination (43).

Rituximab has not been studied in the setting of breast-feding, so alternative agents should be considered. Because of the molecular weight of the medication, only a small amount of the medication is expected to pass into breast milk (14).

Intravenous immunoglobulin (IVIG)

IVIG is a FDA pregnancy class C medication. A small study of IVIG in pregnant women with pemphigus showed improvement in the majority of treated patients. This study had an average of 11.6 years of long-term follow-up where no adverse effects of IVIG were observed in the mothers or children (44). IVIG has also been used successfully as a steroid-sparing agent in antepartum pemphigoid gestationis (45). Interestingly, data suggest that IVIG enhances in vitro fertilization and improves chance of pregnancy in patients with antibody-mediated disease, which is thought to contribute to up to 10% of cases of infertility (44). Recently, a study of 16 Anti-Ro/La-positive pregnant women showed IVIG prevented recurrent neonatal lupus in some cases, and was found to be safe (46). IVIG is used to treat other immunodeficiency syndromes and autoimmune diseases in pregnancy. IgG crosses the human placenta in significant amounts only when gestational age is greater than 32 weeks. IVIG is thought to be a safe option for patients and compatible with pregnancy.

IgG is a normal component of breast milk and IVIG is reported as compatible with breast-feeding and no adverse effects have been reported (14).

Plasma exchange/plasmapheresis

Plasmapheresis or plasma exchange is used to remove immunoglobulins and immune complexes from the circulation and can be efficacious in the setting of autoantibody-mediated disease. It is used for severe autoimmune bullous disease and safe use was reported once in a 30-year-old woman with severe pemphigoid gestationis (47).

Medications commonly used in autoimmune skin disease that are contraindicated in pregnancy

Methotrexate

Methotrexate is an abortifacient and teratogenic agent and is thus not considered safe in pregnancy and is classified as FDA pregnancy category X (48–50). A literature review examining 101 reported cases of methotrexate-exposed pregnancies, at doses ranging from 5 to 25 mg/week, showed a 23% abortion rate and >5% anomaly rate. Anomalies were also seen in fathers taking methotrexate at the time of conception (51). Many authorities recommend that methotrexate should be discontinued for at least 3 months prior to pregnancy in men and women, and folate should be prescribed to women and continued throughout pregnancy. Early folate supplementation is needed to prevent neural tube defects as the neural tube closes during the fifth week of pregnancy, 3 weeks after conception. Finally, excretion in breast milk is known to occur and breast-feding is also contraindicated (4,20,48,51).

Mycophenolate mofetil (MMF)

Although like azathioprine, mycophenolate mofetil (MMF) is FDA category D, human experience suggests that the risks outweigh the benefits for MMF, but not azathioprine. MMF should be discontinued 6 weeks before becoming pregnant to avoid the known teratogenic effects (52). MMF is known to readily cross the placenta and exposure during embryogenesis leads to an increased rate of spontaneous abortions and congenital malformations, at reported rates ranging from 20 to 60%. MMF embryopathy has a distinct tetrad abbreviated as the EMFO tetrad for ear abnormalities (microtia and auditory canal atresia), mouth abnormalities (cleft lip and palate), finger abnormalities (brachydactyly, fifth fingers, and hypoplastic toenails), and organ abnormalities (cardiac, renal, central nervous system, diaphragmatic, and ocular) (53,54). The FDA has issued a black box warning on the teratogenicity of MMF. Lactation is contraindicated because of the lack of data regarding excretion into breast milk or effect if ingested by infants (4,20).

Cyclophosphamide

Cyclophosphamide is an alkylating agent that is commonly used for treatment of vasculitis and

Table 1. Recommendations for management of autoimmune skin diseases in pregnancy

Disease	Recommendations
Cutaneous lupus erythematosus	Skin-directed therapy: low-/mid-potency topical steroids and/or calcineurin inhibitors for mild and skin limited disease. Limited use of potent topical steroids if can be used as systemic steroid-sparing agent. Systemic therapy: Hydroxychloroquine, <6.5 mg/kg/day. Advocate for continued treatment in women with systemic symptoms (arthritis, constitutional symptoms) who become pregnant to avoid risk of flare. Special consideration of use of hydroxychloroquine in women with history of prior cardiac neonatal lupus transmission as it may decrease risk of recurrent transmission. Add azathioprine if no improvement with HCQ.[a]
Dermatomyositis	Limited use of potent topical steroids if can be used as systemic steroid-sparing agent. Skin-directed therapy: low-/mid-potency topical steroids and/or calcineurin inhibitors for mild and skin limited disease. Systemic therapy: Hydroxychloroquine, <6.5 mg/kg/day. If muscle or lung involvement: Corticosteroids at lowest effective dose for rapid control. Azathioprine for cases requiring a maintenance dose of more than 20 mg of prednisone daily.[a,b] Consider IVIG for refractory cases.
Morphea and systemic sclerosis	Plaque morphea not involving the face or joint: Topical corticosteroids at the lowest effective potency, or topical tacrolimus or topical imiquimod (58)[d]. NBUVB if no response.[c] Morphea involving face or crossing joint: Start with NBUVB[c] and switch to systemic corticosteroids if no response. Generalized morphea: NBUVB[c], switch to systemic corticosteroids if no response. Systemic sclerosis: Corticosteroids at lowest effective dose. Consider azathioprine or cyclosporine for cases requiring more than a maintenance dose of 20 mg of prednisone daily in consultation with Rheumatology.[b]
Pemphigus vulgaris	Limited use of potent topical steroids if can be used as systemic steroid-sparing agent. Skin-directed therapy: low-/mid-potency topical steroids and/or calcineurin inhibitors for mild and skin limited disease. Systemic therapy: Corticosteroids at lowest effective dose. Azathioprine for cases requiring more than a maintenance dose of 20 mg of prednisone daily.[a,b] Consider dapsone, IVIG or rituximab for refractory cases.
Pemphigus foliaceus	Treat like pemphigus vulgaris Patients with photodistributed lesions can be treated with hydroxychloroquine, <6.5 mg/kg/day (59)
Pemphigoid gestationis	Limited use of potent topical steroids if can be used as systemic steroid-sparing agent. Skin-directed therapy: low-/mid-potency topical steroids for mild. Systemic therapy: Corticosteroids at lowest effective dose. Azathioprine or IVIG for cases requiring more than a maintenance dose of 20 mg of prednisone daily.[a,b] Consider rituximab or plasmapheresis for refractory cases.

[a]Lactation: consider discarding breast milk excreted within the first 4 hours of taking azathioprine to minimize risk of fetal transmission.

[b]Most patients will require higher doses of prednisone when initiating therapy to control the disease followed by efforts to taper to the lowest effective dose. When the disease is not controlled with a maintenance dose of 20 mg of prednisone daily other agents should be considered

[c]Consider checking folate levels while undergoing phototherapy.

[d]Topical imiquimod has also been used in morphea, and reports of uses in pregnancy, although limited, suggest it is safe.

HCQ, hydroxychloroquine; IVIG, intravenous immunoglobulin; NBUVB, narrow band ultraviolet B.

lupus nephritis. Antenatal exposure to cyclophosphamide early in pregnancy in many animals is associated with craniosynostosis, facial anomalies, distal limb defects, and developmental delay. It is absolutely contraindicated in the first trimester, but it can be used in latter half of pregnancy in situations where the life and health of mother is at risk (i.e., breast cancer in pregnancy). There are rare reports of successful use of cyclophosphamide during pregnancy in lupus without complications (55,56). There have been cases of use in the second and third trimester in lupus patients with fetal demise. For these reasons, cyclophosphamide is considered a FDA pregnancy category X medication and lactation is contraindicated (4).

Incidental exposure

If a patient becomes pregnant while on one of these high-risk medications, consultation with a specialist with experience with these issues is warranted. Noninvasive techniques such as fetal ultrasound may help prevent the unjustified termination of wanted pregnancies.

Over the counter medications: Nonsteroidal anti-inflammatory drugs (NSAIDS) and aspirin

Patients with autoimmune skin disease may consult their dermatologist regarding the use of over-the-counter medications. Aspirin is often recommended for the antiphospholipid antibody syndrome, along with low-molecular weight heparin. The treatment of the antiphospholipid antibody syndrome is outside the scope of this article and consultation with a specialist is indicated; however, it is important for dermatologists to know that low-dose aspirin is felt to not pose a threat to the fetus in the setting of antiphospholipid antibody syndrome (5). Aspirin should be stopped prior to delivery to prevent the possibility of premature closure of the ductus arteriosus (57).

Patients may also want to use over-the-counter NSAIDS agents for some of the constitutional symptoms of their disease. There is evidence that NSAIDs can cause placental insufficiency and impair implantation around the time of conception. They are not recommended in the first trimester and should be used sparingly before 24 weeks gestation. NSAIDS can also result in premature closure of the ductus arteriosus, and thus they are contraindicated in the third trimester (16). NSAIDs can also worsen hypertension and fluid retention of pregnancy (2).

Treatment recommendations

Table 1 summarizes recommendations for treatment by disease.

Conclusions

When facing autoimmune skin disease in young women who are pregnant or plan to be pregnant, one needs to take into consideration the safety and efficacy of the treatment approach. While the vast majority of medications are not deemed completely safe in pregnancy, some are safe enough to warrant use. This requires weighing the risks and benefits of a specific medication and is the focus of this review.

The available data to make these recommendations are inherently limited. While the retrospective population-based studies provide data from large numbers of patients, they rely on registry data and usually lack compliance data. Case reports are biased toward negative results. Such studies are not able to examine important confounders like disease activity and are not designed to evaluate parameters such as trimester of exposure. Further study, including participation in national registries like the OTIS Autoimmune Diseases in Pregnancy Project (OTIS, 877-311-8972 toll-free, http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/), will help improve the availability of data and help inform better clinical decisions (15).

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