Do Safe and Effective Treatment Options Exist for Patients With Active Pemphigus Vulgaris Who Plan Conception and Pregnancy?

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Clinical Question: A 32-year-old woman with active pemphigus vulgaris (PV) who planned to conceive in the near future presented to our dermatology clinic to discuss pharmacologic management of her PV. At that time, she had stable but persistent oral disease while prescribed a regimen of prednisone, 7.5 mg/d; dapsone, 50 mg twice daily; and methotrexate, 25 mg/wk. The objective of this article is to evaluate available evidence regarding the safety and efficacy of steroid-sparing agents in PV during the peripartum period.

Background

Pemphigus vulgaris in pregnancy is rare, with fewer than 40 cases documented in the literature. Avoidance of immunosuppressive medications in patients with PV during pregnancy has been recommended, but this cannot be achieved in many cases because inadequate treatment of PV can contribute to marked patient morbidity and mortality. Moreover, severe maternal disease and high serum antibody titers previously have been correlated with poor neonatal outcomes in a case series of 9 patients. As the first-line treatment for PV, prednisone has a well-established safety record in pregnancy, as well as a rapid onset of action and a high degree of physician comfort with use. Even though prednisone and its metabolites cross the placenta sparingly when compared with other, less frequently used corticosteroids (eg, dexamethasone and betamethasone), high dosages can increase fetal risk for low birth weight, prematurity, infection, and adrenal insufficiency.

Azathioprine (US Food and Drug Administration [FDA] pregnancy category D medication), the most widely used steroid-sparing agent in PV, was the focus of our investigation. Several other steroid-sparing agents (ie, mycophenolate mofetil, cyclophosphamide, and methotrexate) are strongly discouraged or contraindicated in pregnancy. Although cyclosporine (US FDA pregnancy category C) is perhaps the safest corticosteroid-sparing agent in pregnancy, it is believed to be less effective in the treatment of PV than other therapies (K.K.M., personal observations).

Literature Search

With the assistance of the Gundersen Lutheran Medical Library staff and volunteers, we searched the English-language literature using the PubMed database for relevant articles using various combinations of the following search terms: pemphigus vulgaris, neonatal pemphigus vulgaris, immunobullous, azathioprine, dermatology, immunosuppression, and pregnancy. Bibliographies of relevant articles were cross-referenced to expand our search.

Appraisal of the Evidence

As anticipated, no relevant prospective studies or cohort studies were found. We synthesized data from approximately 20 case reports and series reporting over 30 unique patients with PV in pregnancy. Although we found general treatment recommendations of PV in pregnancy published in association with a case report of PV, we did not identify any systematic reviews of the use of steroid-sparing agents in dermatologic conditions during pregnancy.

The safety profile of immunosuppressive medications has been investigated extensively in fields other than dermatology. Conclusions from representative review articles from various medical fields and a set of pregnancy treatment guidelines from the renal transplantation literature were incorporated into our evidence appraisal.

- Prior case studies and case series have described various pharmacological approaches to treating PV in pregnancy, including treatment with oral corticosteroids alone, azathioprine with systemic corticosteroids, dapsone with systemic corticosteroids, topical therapies with or without systemic corticosteroids, and plasmapheresis with systemic corticosteroids. With some exceptions, adverse outcomes (ie, neonatal pemphigus or death) tended to be associated with severe maternal disease and high maternal, neonatal, or umbilical cord serum antibody titers. No consistent association between maternal treatment regimen and fetal outcome was observed.
• Four previous case reports describe the use of azathioprine during pregnancy in patients with PV. Adverse fetal outcomes were associated with each of these pregnancies, with 2 resulting in self-limited neonatal PV\(^3,9\) and 2 ending in stillbirth.\(^13,16,18\) In each of these cases, the mother had severe disease, which may be an independent risk factor for neonatal PV and fetal death.\(^2,3\)
• Preconception initiation of azathioprine in PV was documented in 1 report.\(^9\) In this case, the authors’ treatment approach was to keep the dosages as low as possible (azathioprine, 15 mg/d; prednisone, 15 mg/d) to minimize possible teratogenic effects on the developing fetus.\(^9\)
• Although azathioprine has been linked to congenital malformations in animals, well-documented experience in other fields (eg, transplantation medicine, rheumatology, gastroenterology, and obstetrics) has not demonstrated teratogenicity of azathioprine in humans.\(^6,7,14\) Expert consensus is that azathioprine is a reasonable treatment modality for pregnant patients requiring steroid-sparing agents for serious medical conditions.\(^6,7,15\)

**Limitations of the Critically Appraised Topic**

Although azathioprine has been used for over 30 years in dermatologic conditions, its use during conception and early pregnancy has not been evaluated systematically within the field of dermatology. In part, this may be because dermatologic diseases requiring immunosuppressive medications are relatively uncommon during pregnancy.\(^20\) In addition, several immune-mediated dermatoses of pregnancy, such as pemphigus gestationis and polymorphic eruption of pregnancy, typically arise after the first trimester, a critical period in fetal development.\(^20\) Conclusions regarding the use of steroid-sparing agents in patients with PV in pregnancy are limited because the only available evidence is contained within case reports and series.

**Clinical Bottom Line**

In patients with active PV desiring to conceive:

1. Corticosteroids remain the first-line agent for treatment of PV in pregnancy when low dosages are sufficient for disease control. As the most widely used corticosteroid in dermatology, prednisone (and its metabolites, such as prednisolone) crosses the placenta barrier less readily than other corticosteroid medications. High levels of corticosteroids have been associated with adverse fetal outcomes, however.
2. When unacceptably high levels of corticosteroids are required to achieve disease control, the use of steroid-sparing immunosuppressive medications may become necessary.
3. The paucity of relevant data in the literature requires that decisions regarding the use of steroid-sparing medications in immunobullous dermatoses during pregnancy be based primarily on a collection of published individual experiences.
4. Adverse pregnancy outcomes (ie, neonatal pemphigus and perinatal death) seem to be correlated more closely with poor maternal disease control and higher maternal serum and umbilical cord blood antibody titers than with particular medications used to treat maternal PV.
5. Azathioprine, an FDA pregnancy category D medication with an established record of safety in humans in other medical fields, may be a reasonable agent to employ when adjunct immunosuppression is required in pregnant women with PV.

**What Happened to Our Patient?**

We selected azathioprine as the primary immunosuppressive agent in our preconception management strategy. Because of its relatively slow onset of effect, we decided to initiate therapy several months prior to conception to allow sufficient time for clinical response and disease stabilization. This would enable us to reserve more rapidly acting corticosteroids for disease flares during pregnancy.

Unlike a previously reported patient treated with a very low dose of azathioprine (15 mg/d) in conjunction with prednisone prior to conception,\(^1\) our patient was started on an azathioprine dosage consistent with that usually considered to be in the therapeutic range (75 mg/d) to treat the disease aggressively from the outset of conception planning. Dapsone and methotrexate were tapered and discontinued over the ensuing months. She was maintained on a regimen of prednisone, 7.5 mg/d. With a PV antibody titer of 1:160 and stable mucosal disease, she conceived within several months after discontinuing use of oral contraceptives.

Throughout pregnancy, she experienced mild persistent erythema of the oral mucosa but rarely developed intraoral bullae. She did not develop cutaneous involvement. Following an uneventful pregnancy, she delivered a healthy, full-term female infant with no mucocutaneous disease. At delivery, the maternal cell surface IgG antibody titer was 1:40, whereas the titer for umbilical cord blood cell surface IgG antibody was negative. After 3 years of follow-up, the child continues to grow and develop normally without evidence of any immunologic or other abnormality. We hypothesize that in our patient, adequate treatment of her PV with azathioprine and prednisone minimized passive PV antibody transmission to the fetus, thereby minimizing risk for neonatal PV or death.

**REFERENCES**

8. Terpstra H, de Jong MC, Klokke AH. In vivo bound pemphigus antibodies in a