Iatrogenic Autoimmune Progesterone Dermatitis Caused by 17α-hydroxyprogesterone Caproate for Preterm Labor Prevention

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Preterm birth is the leading cause of perinatal morbidity and mortality in otherwise healthy infants, and the rate of pregnancies complicated by a premature delivery continues to rise. Subsequently, attempts have been made to reduce this rate by using progesterone supplementation during pregnancy. 17α-Hydroxyprogesterone caproate (17P), a metabolite of progesterone, also has been used as supplementation during pregnancy to prevent preterm births. We report a case of iatrogenic autoimmune progesterone dermatitis (APD) in a pregnant woman who received 17P therapy. Due to the increased use of 17P, our case could represent an increasingly prevalent entity that dermatologists and obstetricians should recognize. In this article, we discuss our findings and provide a basic review of APD.

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Preterm birth complicates 12.7% of births in the United States, and despite advances in other fields of medicine, this rate continues to rise. It is the leading cause of perinatal morbidity and mortality in otherwise healthy infants.[1,2] Both maternal morbidity and mortality are inversely proportional to gestational age at delivery.

Medical efforts to decrease the rate of preterm births have largely focused on primary prevention through optimal prenatal care.[3] Many interventions such as tocolytics (medications used to suppress labor) have proven ineffectual or marginally effective. 17α-Hydroxyprogesterone caproate (17P), however, has been shown to be effective secondary prevention.[3]

We report a case of iatrogenic autoimmune progesterone dermatitis (APD) in a pregnant woman receiving 17P. According to a PubMed search of articles indexed for MEDLINE using the terms *autoimmune progesterone dermatitis*, *progesterone dermatitis*, and *17α-hydroxyprogesterone caproate*, no prior cases of APD caused by 17P were reported in the English-language literature. However, with the increased use of 17P, this outcome could represent an increasingly prevalent entity that dermatologists and obstetricians should recognize.

Case Report

A 30-year-old woman (gravida 2, para 1) whose first child was delivered prematurely presented to the dermatologist for a recurrent expanding exanthem that developed 4 days after her third 17P injection. The symptoms began after the first injection as a local-site reaction and then returned after the second injection as a mild maculopapular exanthem proximate to the injection site. At the time of presentation, the reaction had recurred as a more expansive, pruritic, and urticarial exanthem on the abdomen, arms, and buttocks. Biopsy of the exanthem showed lymphoplasmacytic dermatitis with eosinophils consistent with chronic urticaria.

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Direct immunofluorescence examination was negative. Injections of 17P were stopped and the patient's exanthem resolved within 7 days. No flares or recurrences occurred and the child was delivered at 38 weeks with no sequelae.

Comment

Our case is indicative of the acute iatrogenic form of APD that is not of the usual cyclical nature or induced by the typical medications but rather secondary to 17P. Progesterone compounds have been studied since the mid-1960s in the hope of decreasing preterm labor. In 1989, a meta-analysis of studies of the general population showed no benefit for progesterone in reducing preterm birth, though some studies did show potential benefit in higher-risk groups.[4] The National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, however, later performed a large multicenter, randomized, controlled trial of weekly intramuscular injections of 17P in women who had prior singleton preterm deliveries.[3] The treatment group was found to have a significantly reduced risk for preterm delivery at less than 37 weeks of gestation (incidence, 36.3% vs 54.9% [$P<.001$]; relative risk, 0.66 [95% confidence interval, 0.54-0.81]) and a 42% reduction in the rate of delivery before 32 weeks of gestation (11.4% vs 19.6% [$P=.02$]). There also were significantly lower rates of preterm delivery complications in the infants of the treated group.[3] The 17P injections contain only sterile 17α-hydroxyprogesterone in solution with the fatty acid ester caproate and no additives. In the study, only minor side effects, including soreness, swelling, and local injection-site reactions, were reported.[3] The American Congress of Obstetrics and Gynecology still recommends the use of 17P in women with a documented history of spontaneous birth at less than 37 weeks of gestation,[5] though additional studies are underway to further evaluate the efficacy of 17P in different populations.[6-8]

Typically, APD refers to a rare disorder characterized by cyclical cutaneous eruptions that occur at the luteal phase of the menstrual cycle during which there is a marked increase in endogenous progesterone production.[9] These eruptions occur as type I immediate and type IV delayed hypersensitivity reactions. It has been postulated that these reactions occur secondary to hypersensitivity developed from prior exogenous progesterone exposure or possibly from a cross-reaction between endogenous progesterone and antibodies formed against other antigens such as viral infections, medications, or food products.[10] Alternatively, the elevated levels of progesterone may exacerbate hypersensitivity reactions through a metabolic effect rather than an immunologic reaction.[11] A report of familial APD revealed that a genetic component also may exist.[12]

Autoimmune progesterone dermatitis often presents as a chronic urticarial reaction but can manifest in a variety of ways to include eczema, erythema multiforme, stomatitis, and vesiculobullous eruptions.[13] A case of APD presenting with purpura and petechiae also has been reported.[14] Most patients are women in the third and fourth decades of life who report prior exposure to exogenous progesterone such as in oral contraceptives,[10,13] hormone replacement therapy,[15] or even intrauterine contraceptive devices.[16] Infertility treatments also have been reported as the cause of APD.[17] Not well-reported, however, are cases of APD resulting from the metabolites of progesterone, such as 17P. In our case, due to the quick resolution of the worsening exanthem after stopping the 17P injections, acute iatrogenic induction of APD should be considered. Cases of APD also have been reported in women[10,18,19] and adolescent girls[20] without prior exposure to synthetic progesterone, and these cases can begin spontaneously or are associated with pregnancy. In addition, APD progressing to systemic anaphylaxis has been reported.[13,21]

The cyclical and premenstrual nature of classic APD makes clinical diagnosis possible, though patients with irregular menses, such as those with endometriosis, may have irregular symptoms.[22] The diagnosis can be confirmed through an intradermal injection of progesterone that yields a positive reaction or by resolution of symptoms after treatment to inhibit ovulation. The sensitivity test also has been conducted through intramuscular, oral, and intravaginal routes.[23] Acute iatrogenic hypersensitivity, as in our case, is confirmed by treatment-associated symptoms and resolution upon cessation of the offending agent. When APD presents as an immediate hypersensitivity reaction to exogenous progesterone, as in our case, the physician must weigh the risks and benefits of therapy, as treatment consists of cessation of the offending drug.

Histopathologic examination of cutaneous involvement shows the typical pattern of urticaria, though biopsy in one case showed features of both erythema multiforme and urticaria, and the patient's symptoms responded to antihistamines.[24] Patch testing may produce false-negative results,[25] but the enzyme-linked immunosorbent spot assay for monitoring immune responses may be useful in diagnosis.[26] First-line treatment in cyclical APD is suppression of ovulation with appropriate oral contraceptives, but gonadotropin-releasing hormone/luteinizing hormone analogues, danazol, tamoxifen, and bilateral oophorectomy also are effective.[10]

Conclusion

Despite medical advancements, pregnancies complicated by premature delivery continue to increase. Some studies, however, have shown that progesterone supplementation, more recently consisting of the metabolite 17P, reduces preterm birth in women at risk. However, due to the increased use of progesterone and its metabolites as well as the possibility of inducing a hypersensitivity reaction capable of producing anaphylaxis, dermatologists and obstetricians should be aware of APD and its iatrogenic causes.

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