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Spontaneous abortion during ustekinumab therapy

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Abstract

Background: Psoriasis affects a considerable proportion of women in their reproductive years. Limited published data exist about the possible negative impact of the disease itself in the prognosis of pregnancy. On this background, the emergence of newer biologic agents for psoriasis treatment — such as ustekinumab — raises safety issues concerning the exposure to the drug during pregnancy. To our knowledge this is the first report in the literature describing a pregnancy outcome under ustekinumab treatment.

Observation: We report a 35-year-old female psoriasis patient who was under treatment with ustekinumab for a year when she inadvertedly became pregnant. The drug was discontinued immediately and the patient did not opt for termination. During the 12th week of gestation she experienced a spontaneous abortion.

Conclusion: Although the patient's profile fulfilled 2 general risk factors for spontaneous abortion — she was a smoker and this was her third pregnancy — one could not underestimate the possible role of the drug and of psoriasis per se in this adverse pregnancy outcome. Pregnancy registries and large prospective studies are needed in order to determine whether poorer pregnancies outcomes in psoriatic women are due to the disease itself, associated comorbidities or side-effects of new therapies such as ustekinumab. (*J Dermatol Case Rep*. 2012; 6(4): 105-107)

Introduction

Psoriasis is an immune-mediated disease that affects a considerable proportion of women in their reproductive years. Although there is a growing awareness about the probable negative impact of the disease in the prognosis of pregnancy, limited published data exist about this significant aspect. On this background, the emergence of new biologic agents for psoriasis treatment raises safety issues concerning the exposure to these drugs during pregnancy. Ustekinumab (Stelara®), a human monoclonal anti-inteleukin 12 (IL-12) and IL-23 antibody, is the latest biologic agent to be officially licensed for psoriasis and there is not one report in the literature dealing with exposures to ustekinumab in pregnancy.

Case Report

We report the case of a 35-year-old female patient with a 10-year history of psoriasis. In the past she has received, intermittently, both topical steroids and cyclosporine. The latter was discontinued due to gingival hyperplasia a month before the initiation of ustekinumab. During the last year she has been treated with subcutaneous injections of ustekinumab 45 mg, following the standard dose regimen (1 injection at weeks 0, 4 and then every 12 weeks). The drug was administered as monotherapy (no other topical or systemic treatment) and the response was excellent (Psoriasis Area and Severity Index (PASI): 14,4 at week 0, PASI: 0 at week 28 — 4th injection). According to the patient's record she was a heavy smoker (>20 cigarettes/day) but she did not suffer from any other comorbidity, including obesity. An unplanned pregnancy occurred, almost 2 months after her fifth injection because the patient did not comply with our advice and had not used any kind of contraception. At that point the drug was discontinued and the patient was fully informed about the possible complications; nevertheless she did not opt for termination. The obstetric file of the patient was excellent with two previous live births and no spontaneous or intended abortions. Unfortunately, despite the fact

that she adopted a healthier way of life — by quitting smoking and not using any amount of alcohol — during the 12th week of gestation she experienced a spontaneous abortion (Table 1).

Table 1. Chronological order of events.

Week 0	1st ustekinumab injection (45 mg sc)
Week 4	2nd ustekinumab injection (45 mg sc)
Week 16	3rd ustekinumab injection (45 mg sc)
Week 28	4th ustekinumab injection (45 mg sc)
Week 40	5th ustekinumab injection (45 mg sc)
Week 42	Last menstruation
Week 52	Patient did not receive the 6th ustekinumab injection due to pregnancy
Week 54	Spontaneous abortion

Discussion

Ustekinumab, is a human monoclonal antibody that selectively binds to the p40 subunit shared by interleukin (IL) 12 and IL-23, and thereby inhibits their biological role in the pathogenesis of psoriasis.[1] It has been officially licensed for the treatment of moderate to severe plaque psoriasis in Europe since January 2009.[2] According to the summary of product characteristics of Stelara it is preferable, as a precautionary measure, to avoid the use of ustekinumab in pregnancy.[2] Thus, women of childbearing potential should use effective methods of contraception during treatment and up to 15 weeks after treatment.[2] Although, there are no reports in the literature regarding exposures to ustekinumab during pregnancy, unpublished data from clinical studies quote that, as of June 2010, 42 maternal exposures were identified across all clinical studies of ustekinumab (protocol deviations).[3] In all of these pregnant women the drug was discontinued so the embryonic/foetal exposure was expected to be limited taking into consideration that the transplacental transport of ustekinumb, a large IgG molecule, is poor until the late second or early third trimester of pregnancy.[4] Ten of these pregnancies resulted in live births with no defects or adverse events; six resulted in a spontaneous abortion, eight were elective terminations, two had live births with other adverse events and sixteen had an unknown outcome.[3] Developmental toxicology studies found that administration of high doses of ustekinumab during pregnancy and lactation in the cynomolgus macaque monkeys produced no adverse events on the pregnant females and no adverse effects on the infants.[5] Moreover, the pregnancy losses that occurred in all these studies were similar between the control group and the ustekinumab treatment groups and were also similar to the historical background control data for the testing facility.[5]

Ustekinumab, like tumor necrosis factor α (TNFα) antagonists, is classified as a Pregnancy Category B drug, indicating that although no risk is apparent from animal studies, there are no controlled studies of female patients receiving these agents, and therefore it is not known if ustekinumab can cause fetal harm if administered to a pregnant female or if the drug can affect reproductive capacity. Data regarding the impact of anti-TNFα agents on pregnancy outcomes is derived mainly from rheumatology and gastroenterology reports and retrospective collections. Despite the fact that the majority of these cases reported rather reassuring results, a recent prospective collection of pregnancy outcomes, in women with arthritis-related diseases exposed to anti-TNF therapy, suggested that treatment with these drugs at the time of conception may be associated with an increased risk of spontaneous abortion, while the role of disease severity and other anti-rheumatic treatment could not be excluded.[6]

Psoriasis per se, on the other hand, is mentioned in the obstetric literature as a risk factor for increased rate of pregnancy complications such as spontaneous abortions, recurrent pregnancy losses, failure to conceive, preterm deliveries.[7,8] Several theories have been developed regarding the mechanism of this association. For instance, it is possible that pro-inflammatory cytokines such as Tumor necrosis Factor a (TNFα), Interleukin-6 (IL-6) and Interferon-γ (INFγ) which are elevated in the sera and psoriatic skin have detrimental effects on the maternal placenta and could thus lead to adverse pregnancy outcomes.[9,10] On the other hand psoriasis is associated with certain co-morbid conditions such as obesity, hypertension, diabetes mellitus, dislypidemia, depression and other maternal risk behaviors such as smoking and alcohol consumption all of which could badly influence pregnancy outcomes.[11] In dermatology fields, few retrospective studies exist examining pregnancy outcomes among psoriasis patients and their results are rather conflicting. Cohen-Barak *et al* argued that moderate-to-severe psoriasis is associated with higher prevalence of spontaneous and induced abortions while Seeger *et al* reported no differences in pregnancy incidence, spontaneous and induced abortions and stillbirths between psoriasis and control groups.[12,13]

In our case one should not exclude the possibility that this spontaneous abortion fell into the rate of abortions (25%) taking place in the general population.[14] Moreover, there seems to be an inherent increase in risk of complications in successive pregnancies, albeit our patient completed her second pregnancy 7 years prior to the last.[15] Also, the fact that our patient was a heavy smoker, although she stopped smoking after she discovered that she was pregnant, could be implicated in the adverse pregnancy outcome.

Conclusion

As a conclusion, pregnancy registries and large prospective studies are needed in order to determine whether poorer pregnancies outcomes in psoriatic women are due to the disease itself, associated comorbidities or side-effects of new therapies such as ustekinumab.

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