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SPECIAL ARTICLE

Psoriasis and its management in women of childbearing age: tools to increase awareness in dermatologists and patients

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ABSTRACT

Psoriasis is a common, chronic inflammatory disease with a multifactorial pathogenesis. Mean age at presentation of psoriasis is 28 years in women, which is almost the height of fertility age. Since women of childbearing potential represent a significant proportion of psoriatic patients, the impact of psoriasis and its treatment on fertility, pregnancy, and breastfeeding should be highlighted for a proper management. Therefore, when approaching to a psoriatic woman of childbearing age, Healthcare Providers should be adequately informed and ready to provide the patients with answers to the most frequently asked questions. The Italian Society of Dermatology and Venereology (SIDeMaST) has fostered a Task Force named "Psoriasis in Women of Childbearing Age" which is composed by a group of Italian female dermatologists with a high expertise in psoriasis treatment. The aims of the Task Force are to increase awareness of the disease and its treatment in patients of childbearing age among both dermatologists and women affected by psoriasis and to encourage counselling on family planning. With the aim of providing a real support for the proper management of the delicate journey to motherhood, the Italian Task Force has published two different informative booklets addressed to patients and dermatologists which focus on the main issues regarding psoriasis in women of childbearing age.

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KEY WORDS: Psoriasis; Age factors; Women; Health communication.

Psoriasis is a common, immune-mediated inflammatory disease with a chronic course and a multifactorial pathogenesis, which manifests as red, scaly, itchy and/or painful patches and plaques.

Psoriasis is part of the immune-mediated inflammatory diseases (IMIDs) and it is characterized by a systemic inflammation with a potential multi-organ involvement and a significant increased risk of comorbidities.[1] Up to 40% of psoriatic patients develop psoriatic arthritis (PsA), typically within 5 to 10 years after cutaneous manifestations.[2]

The prevalence of psoriasis varies worldwide, ranging between 0.09% and 11.43% in different countries, making thus psoriasis an important global problem with at least 1% to 3% of white population affected, without significant differences in prevalence between women and men.[3] Age-specific incidence rates typically demonstrate a dual peak: 'early onset' psoriasis, categorized as being diagnosed earlier than 40 years of age, shows clear differences between sexes with females being more likely to be diagnosed at an earlier age. The peak of early-onset psoriasis in women indeed occurs in the late teens and early twenties.[4] In detail, in women, the mean age of psoriasis onset is 28 years, which is almost the height of fertility age.[5] "Late-onset" psoriasis, categorized as being diagnosed later than 40 years of age, instead, shows little difference in distribution between males and females. Since women of childbearing potential represent a significant proportion of psoriatic patients, the influence of psoriasis on fertility and pregnancy should be considered and properly approached.

Psoriasis and fertility

Literature data regarding the possible impact of psoriasis on women's fertility are still controversial.

Though psoriasis does not seem to directly affect fertility, a 22% lower likelihood of pregnancy has been reported among psoriatic women compared to the general population and systemic inflammatory state has been thought to be primarily responsible for the overall reduction of pregnancies.[6]

In a recent Danish study, no significant differences in time to become pregnant has been reported in patients with psoriasis compared to "healthy" women; however, the study had some limitations since it was conducted through telephone interviews and diagnosis of psoriasis was self-reported without any information on the severity of the disease and treatment. In addition, the Authors did not consider women and patients who never became pregnant, since the study was based on data from the Danish National Birth Cohort.[7]

In contrast, a USA study observed significantly fewer births than expected in mothers with severe psoriasis.[8] Recently, in women of childbearing age with moderate-to-severe psoriasis, the fertility age-standardized rate has been found to be less than half the fertility rate for women of the same age in the Spanish population.[9]

The role of systemic inflammation in inducing primary and secondary hypogonadism has been described. Several pro-inflammatory cytokines, such as tumor necrosis factor (TNF) alpha, interleukin (IL)-6 and IL-1, have been found to play a central role in the inhibition of the reproductive axis, mainly through a potent inhibition of the hypothalamic-pituitary gonadal axis.[10]

A recent study in a Turkish psoriatic female population has found significant sexual hormone alterations as a sign of an impaired ovarian reserve. In fertility clinics, the ovarian reserve, which is evaluated by several parameters, including follicle-stimulating hormone (FSH) levels and antral follicle count (AFC) represents the number of primordial follicles and is an indicator of fertility in reproductive-age women. In particular, the study analyzed 14 women with psoriasis and 35 healthy age- and Body Mass Index-matched controls and found that patients with psoriasis had significantly higher serum level of FSH and FSH-to-luteinizing hormone (LH) ratio than healthy controls. In the same study, the AFC was significantly lower in psoriasis patients than in healthy subjects, suggesting that women with psoriasis may have a diminished ovarian reserve.[11] However, another study conducted on 36 women with psoriasis and 36 healthy controls found no significant differences in AFC between the two groups, while anti-Mullerian hormone serum levels and mean ovarian volumes were slightly lower in psoriatic women.[12]

It is well known that women with psoriasis have a higher risk of comorbidities such as cardiovascular disease, metabolic syndrome, diabetes and non-alcoholic fatty liver diseases than the general population and that each of these comorbidities or even their association may negatively affect fertility.[13]

Furthermore, a reduced fertility may be considered a consequence of some unhealthy behaviors which are quite common in female psoriatic patients.[14] In this regard, a random effect meta-analysis found an association between psoriasis and current smoking (odds ratio [OR] 1.78; 95% CI: 1.52-2.06), as well as between psoriasis and former smoking (OR=1.62; 95% CI: 1.33-1.99).[15] A study conducted in 1998 described that women who smoked had a significantly higher OR of infertility (OR=1.60; 95% CI: 1.34-1.91), compared to non-smokers.[16] This impairment of fertility among female smokers may be probably attributed to a decreased ovarian function and a reduced ovarian reserve. Also, a misfeeding behavior, frequently leading to obesity, could compromise women's fertility. It has been found that women with a BMI higher than 30 have longer time to pregnancy than women with a BMI between 20 and 25.[17]

A common condition in psoriatic women is polycystic ovary syndrome (PCOS), also known as Stein-Leventhal

syndrome, affecting up to 50% of patients, and women with psoriasis and PCOS are more likely to have a more severe skin disease than those with psoriasis alone.[18] It is known that PCOS is a predisposing condition to menstrual irregularity, infertility, but also to several obstetric complications; therefore, its association with psoriasis could represent a real risk for an impaired fertility and adverse pregnancy outcomes in psoriatic women.

However, other important contributing aspects which could account for an overall reduction of pregnancies in psoriatic women could be voluntary childlessness, concern with regard to disease activity during pregnancy or post-partum, fear of the effects of the disease and/or of its therapy on pregnancy, reduced intimacy with the partner due to embarrassment, and/or physical inability to have intercourse because of itch, discomfort, burning, dyspareunia, worsening of genital psoriasis after intercourses or joint pain in case of PsA.[19] A study by Ryan *et al.* has found that psoriasis, particularly in the presence of genital involvement, has relevant psychosexual implications for psoriasis patients.[20] In their study, 63% of patients had a current and/or previous history of genital involvement with 87% reporting itch, 39% pain, 42% dyspareunia, 32% worsening of their genital psoriasis after intercourses and 43% decreased frequency of intercourses. Additionally, in patients with PsA, muscle-skeletal pain may be an additional cause for a decreased frequency of sexual intercourses.

In conclusion, although evidence suggests an impaired fertility in women with psoriasis, literature data on this topic are still scarce and further larger population-based studies are required.

How does psoriasis influence pregnancy and *vice versa*?

An increasing number of psoriatic women expresses concerns about possible worsening of the disease during pregnancy. Psoriasis is mainly mediated by a T-helper (Th)17 response and, to a lesser extent, by Th1 involvement.[21] The estrogen/progesterone-mediated downregulation of Th17 and Th1 immune responses that occurs during pregnancy, aiming to prevent fetal rejection, usually leads to improvement of psoriasis, as reported in most women (55%). However, since a proportion of psoriatic women experiences no change (21%) or even worsening (23%) of the disease during pregnancy, the course of psoriasis[22, 23] is indeed unpredictable. Moreover, many women (40-90%) experience worsening of their disease in the post-partum period.[24]

It is conceivable that, in women with active psoriasis during pregnancy, systemic inflammatory and immune dysregulation could potentially affect the physiological progression of pregnancy, as demonstrated in other IMID such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease.[25, 26] However, data regarding the relationship between psoriasis and adverse pregnancy outcomes are still controversial.

Since the serum levels of proinflammatory cytokines are related to the severity of psoriasis, women with moderate to severe disease could be at risk for negative pregnancy outcomes. Several studies have highlighted the relationship between severity of psoriasis and pregnancy outcomes.

Yang *et al.* found that patients with severe psoriasis have an increased risk of low-birth weight newborns[27] while mild to moderate psoriasis, instead, does not seem to be associated with adverse birth outcomes.[27, 28] However, an increased risk of spontaneous abortion in women with moderate to severe psoriasis has been reported in two other studies including small number of patients.[29, 30]

A systematic review of nine observational studies did not demonstrate an increased risk of poor outcomes in pregnant women with psoriasis.[31] On the other hand, a large population-based study conducted on Danish and Swedish registries found an increased risk of gestational diabetes, hypertension, preeclampsia and emergency caesarean delivery in women with psoriasis and preterm birth and low birth weight in newborns from mothers with severe disease.[32] Besides, psoriasis comorbidities such as diabetes, hypertension, obesity, metabolic syndrome, cardiovascular diseases, and depression, which are also related to disease severity and duration, may increase the risk of negative birth outcomes.

Unhealthy behaviors including smoking or alcohol consumption can also influence pregnancy outcomes.[33, 34] Since smoking during pregnancy and maternal overweight/obesity have been related to an increased risk for congenital anomalies, low-birth weight and preterm birth,[14] psoriatic patients should be counselled about these modifiable risk factors. Therefore, avoiding tobacco use, reducing body weight, and taking prenatal folic acid supplements are recommended in psoriatic women of childbearing potential.

Therefore, a treatment plan is necessary when considering women with moderate-to-severe psoriasis who wish to become pregnant in order to find the correct balance between the risk of psoriasis treatments and the risk of an uncontrolled disease.

Management of psoriasis in women of childbearing age

Many treatments for psoriasis are currently available, ranging from topical drugs to systemic agents, with the limitation for many of these of a potential teratogenic effect when used in pregnant women or in patients of childbearing potential. Almost all topical therapies can be used during pregnancy, except for anthralin or tazarotene, because of their known mutagenic properties. Narrowband ultraviolet B phototherapy is deemed to be safe while P-UVA treatment is contraindicated due to teratogenic properties of psoralen.[35] Among conventional systemic agents, cyclosporine is usually considered compatible with pregnancy, although it is associated with an increased risk of gestational hypertension; methotrexate and acitretin are, instead, strictly contraindicated.[36]

Several data are recently emerging about safety of targeted biologic anti-psoriatic therapies during pregnancy. All the biologics, except for certolizumab pegol (CZP), an anti TNF-α agent, include in their molecular structure the Fc fragment of a human immunoglobulin. Since the placenta has the receptor for Fc immunoglobulin fragment, named neonatal Fc receptor (FcRn), biologics are actively transferred and reach the foetal circulation. CZP differs structurally from other biologics because it is a humanized PEG-ylated antibody Fab' fragment, lacking the IgG1 Fc portion: for this reason it is not capable to bind the neonatal Fc receptor and it cannot be actively transported across placenta.[37]

CZP is the only biologic agent with clinical trial data supporting its use in pregnancy and breastfeeding.[38] Moreover, data retrieved from UCB Pharma safety database including 1600 CZP-exposed pregnancies were analyzed (1541 maternal and 59 paternal CZP exposures), showed that 85.3% of CZP-exposed pregnancies resulted in live births, and the rate of major congenital malformations for CZP-exposed infants was similar to that reported in the general population.[39] Beyond CZP, reassuring evidence is emerging about safety of other TNF blockers in pregnancy and current psoriasis guidelines emphasize that the decision of discontinuation of these drugs during pregnancy should be made on patient-by-patient basis.[40] A recent study on safety of biologics for psoriasis during pregnancy recommends that infants born to mothers treated with TNF inhibitors during pregnancy should not receive live vaccinations for at least 6 months after birth due to an increased risk of infections.[41] Limited data are available about the use of newer anti-ILs antibodies in pregnant women. A recent analysis of maternal or paternal exposure to the anti-IL-17A secukinumab based on Novartis global safety database showed no signs of poor pregnancy and neonatal outcomes.[42] Furthermore, data from the Janssen Biotech safety database identified no significant risk of spontaneous abortions and congenital abnormalities in women with psoriasis, PsA or Crohn disease exposed to ustekinumab during pregnancy or within 2 months prior to conception.[43] To date, no data regarding safety of anti-IL-23 or anti-IL-17RA agents in pregnant women are reported.

How aware are dermatologists and patients?

In clinical practice, when approaching a psoriatic woman of childbearing age, irrespective of family planning intentions, the dermatologists must consider a number of issues. Unfortunately, dermatologists are sometimes not properly skilled to assist women with psoriasis or PsA during their journey to motherhood. A patient journey survey of women of childbearing age with psoriatic diseases (PSO: N.=367; PsA: N.=142) revealed that many women had to initiate the discussion about family planning with healthcare professionals (HCPs) — primary care physician, dermatologist, rheumatologist, obstetrician/gynecologist — by themselves and their main fear regarded the possibility to pass on health issues to the child.[44] A National Psoriasis Foundation (NPF) survey, conducted by Lebwohl *et al.* included 65% of whom were currently, or in the future, trying to conceive, 6% were currently pregnant, and 43% had given birth in the last 5 years. Overall, 68% of women who had been pregnant in the last 5 years discussed family planning with their HCP, but only in 7% of patients the discussion was initiated by the HCP; furthermore, 33% of patients delayed informing their treating physicians of their pregnancy and 20% did not tell them at all. Moreover, a lack of information on how to manage psoriasis during pregnancy emerged from the US NPF survey, in which 65% of patients who had been pregnant stopped treatment, taking the decision by themselves in 24.4% of cases; 33% of this group did so due to misinformation regarding treatment compatibility with pregnancy.[45]

A national observational multicentric survey was conducted in France in 2018 among 152 dermatologists who answered to a specific questionnaire dealing with the concerns of women suffering from psoriasis and the position of dermatologists' in this setting. Overall, the main issue addressed by three-quarters of dermatologists upon psoriasis diagnosis was the patient's wish to become pregnant in the

short-term; only about one-third of dermatologists resulted to be familiar with existing recommendations for psoriasis treatment in child-bearing women. The main problems expressed by patients were the compatibility of psoriasis treatment with pregnancy, disease transmission and fetal risks in 64%, 54% and 49% of women, respectively.[46]

Dermatologists should be aware that the burden of psoriasis for women is extremely high and may have a profound negative impact on their reproductive life planning, potentially leading to deferring pregnancies or to poor management of psoriasis during pregnancy.

In this setting, counselling of psoriatic women during their reproductive years is extremely important and should be part of the physician-patient communication.

Project presentation

In order to highlight the importance of a real commitment of HCPs to a relevant topic such as management of psoriasis in women of childbearing age and during pregnancy, the Italian Society of Dermatology and Venereology (SIDeMaST) has fostered a Task Force named "Psoriasis in Women of Childbearing Age" which is composed by a group of Italian female dermatologists with high expertise in treatment of psoriasis. The members of the Task Force contributed to the writing of two booklets on "Psoriasis and Pregnancy" addressed to dermatologists and patients, respectively.

These booklets have been sent to Italian dermatological centers which prescribe biological drugs for psoriasis and have been distributed through regional and national dermatology meetings; in addition, they can be downloaded from the SIDeMaST website (www.sidemast.org/blog/task-force-sidemast-psoriasi-donna/).

The booklet addressed to the patient provides simple but crucial information concerning most frequent questions on fertility, pregnancy, breastfeeding and, most importantly, encourages counselling on family planning.

The booklet addressed to dermatologists summarizes the key issues related to reproduction in women with psoriasis: it consists of six sections regarding contraception, medically assisted reproduction methods, pregnancy, postpartum period, problems in raising a child, and fertility in men with psoriasis. In the first section of the booklet tables showing contraceptive methods recommended during therapy with systemic antipsoriatic drugs and possible interactions between individual drugs and contraceptive methods are reported. The second section is focused on medically assisted reproduction methods to which the patient can access, after gynecological consultation. The third and fourth sections deal with the course of psoriasis during pregnancy and the first six weeks after delivery (post-partum period), focusing on the possible risks for the fetus and the newborn: tables showing compatibility of topical and systemic treatments for psoriasis during pregnancy and breast-feeding are also available in this section. The fifth section provides suggestions to dermatologists to become the reference HCP for the patient, even when referring her to other specialists for medical and psychological support. Finally, the last section describes fertility in men with psoriasis, in order to offer to a male patient a therapeutic approach that is compatible with his paternity desire, considering that some systemic treatments may potentially affect male fertility.

Through these booklets, the "Psoriasis in Women of Childbearing Age" Italian Task Force aims to raise awareness and update Italian dermatologists about management of psoriasis in this special patients' population; these booklets are also aimed to properly inform the patients, providing answers to frequently asked questions and, hopefully, to promote counselling on family planning.

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Conflicts of interest.—Clara De Simone has served as advisory board member, consultant and speaker receiving honoraria from Almirall, AbbVie, Amgen, Biogen, Celgene, Lilly, LEO Pharma, Janssen, Novartis, Pierre Fabre, Sanofi, UCB Pharma. Anna Balato has served as speaker or board member for AbbVie, Eli Lilly, Sanofi. Serafinella P. Cannavò has served on advisory boards and received honoraria for lectures from AbbVie, LEO Pharma, Celgene, Eli Lilly, Janssen, Novartis, Sanofi-Genzyme. Annunziata Dattola has been a consultant and/or a speaker for UCB, Eli Lilly, LEO Pharma, Medac Pharma. Maria Esposito has served as speaker or broad member for AbbVie, Almirall, Eli Lilly, LEO Pharma, Novartis, UCB, Sanofi-Genzyme. Maria C. Fargnoli has served on advisory boards, received honoraria for lectures and research from Almirall, AbbVie, Galderma, LEO Pharma, Mylan, Medac Pharma, Celgene, Pierre

Fabre, UCB, Eli Lilly, Pfizer, Janssen, Novartis, Sanofi – Genzyme, Roche, Sunpharma, and MSD. Katharina Hansel has served as speaker or board member for AbbVie, Almirall, Celgene, and Novartis. Maria L. Musumeci served as advisory board member and consultant, and has received fees and speaker's honoraria or has participated to clinical trials for AbbVie, Almirall, Biogen, Eli Lilly, Janssen Cilag, LEO Pharma, Novartis. Annamaria Offidani has been principal investigators in clinical trials sponsored by and/or received personal fees from AbbVie, Alfasigma, Amgen, Difa Cooper, Celgene, Eli Lilly, Galderma, Janssen, Laboratori Farmacologici Milanesi, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Regeneron, Sanofi, UCB-Pharma. Aurora Parodi: Novartis, Pfizer, Almirall,Galderma, UCB, LEO Pharma, Eli Lilly, Pierre Fabre, Celgene, Amgen, Unifarco, Janssen Cilag, AbbVie, Menarini. Annalisa Patrizi has served as speaker or consultant or advisory board member for AbbVie, Eli Lilly, Novartis, Pfizer, Almirall, Celgene, Sanofi-Genzyme, LEO Pharma, UCB Pharma, Menarini, Janssen. Ketty Peris reports grants and personal fees for advisory Board meeting from Almirall, AbbVie, Biogen, Lilly, Celgene, Galderma, LEO Pharma, Novartis, Pierre Fabre, Sanofi, Sandoz, Sun Pharma and Janssen, outside of the submitted work. Marina Venturini has served as speaker or board member for AbbVie and Novartis. Francesca Prignano served as consultant, adviser and presenter for Novartis, Eli Lilly, Janssen-Cilag, AbbVie, Biogen, LEO Pharma. Laura Calabrese, Roberta Giuffrida, Maddalena Napolitano, and Giulia Radi have no conflicts of interest.

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