Review

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The impact of gender and sex in psoriasis: What to be aware of when treating women with psoriasis

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ABSTRACT

Background: Psoriasis is a common chronic inflammatory skin disease with an exceptionally high burden for women.

Objective: Sex-dependent differences in disease manifestation, severity, treatment choices, subjective disease perception, and the impact on quality of life and risk factors are described and comprehensively discussed.

Methods: A literature search was conducted using MEDLINE (PubMed) and the Cochrane Library for systematic reviews to investigate the challenges in treating women with psoriasis.

Results and conclusions: The incidence, prevalence, and manifestation of psoriasis of the skin are similar between different sexes. Genetic and environmental factors such as obesity and metabolic syndrome are risk factors and are not equally relevant or pronounced in women and men. Overall, women have a lower disease severity measured by the Psoriasis Area Severity Index, which is associated with a higher impairment of their life quality measured by the Dermatology Life Quality Index compared with men. In addition, women with psoriasis are more likely to have depression than men. Hormonal factors affect psoriasis, with a correlation of high estrogen levels and improvement of psoriasis. Data regarding differences in prescribing patterns of systemic treatments and the severity of psoriasis are not entirely consistent. Registry studies show that men tend to have more severe psoriasis and, in some cases, are prescribed systemic therapies more frequently. Women tend to respond better to systemic treatments and to experience more adverse events. Treatment options are the same for both sexes, except during pregnancy and lactation. Various treatment options are contraindicated due to fear of fetal or neonate harm and lack of data. Topical steroids can be prescribed with a high degree of safety during pregnancy. For other topical therapies (calcineurin inhibitors and vitamin D analogs), no studies of adverse effects in pregnancy are available, and safety data mainly stem from studies examining effects after systemic administration. Antitumor necrosis factor monoclonal antibodies (except for certolizumab pegol) have been associated with a possible increased risk of preterm birth, low gestational age, and cesarean deliveries. Prospective data on the safety of biologics other than antitumor necrosis factor-alpha antibodies to accurately assess whether novel biologics (eg, anti-interleukin 17, 12/23, 23) can be used for systemic therapy in pregnancy are lacking or currently being conducted.

Keywords: Differences, gender, pregnancy, psoriasis

Introduction

Psoriasis is a chronic, inflammatory skin disease with a prevalence of 1% to 4% in countries with a predominantly Caucasian population.[1–5] Sex-dependent differences in epidemiology, disease manifestation, comorbidities, and treatment outcomes were observed in many diseases and are increasingly relevant in medical science.[6–10] Sex-dependent differences were reported for psoriasis disease manifestation, severity, treatment choices, subjective disease perception, and the impact on life quality.[11,12] Understanding such disparities could improve care in women with psoriasis, yield more effective and satisfactory treatment outcomes, and reduce inequalities in care.

Methods

Objectives

This narrative literature review highlights gender and sex-specific aspects and considerations when treating women with psoriasis of the skin.

Search methods

A literature search was conducted through March 3, 2021, using MEDLINE (PubMed) and the Cochrane Library for systematic reviews. The keywords included "gender, sex, female, male, women, woman, men, man, dermatology, psoriasis, prevalence, incidence, hormones, pregnancy, lactation, transplacental, transplacental transfer, quality of life (QoL), mental health, genetic risk factors, HLA-Cw6, psoriasis susceptibility 1 gene (PSORS1), chromosome 6p21, treatment, biologic treatment, biologicals, adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, tildrakizumab, ustekinumab, apremilast, cyclosporine, neotigason, fumaric acid, fumarate, tacrolimus, calcipotriol, and calcitriol." Pivotal papers describing novel insights and society guidelines were considered. Additional studies were found using bibliographical information of relevant articles. To obtain a

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Implications for patients and their families: What is known about this subject regarding women and their families?

- Women of childbearing age can be affected by psoriasis and need effective treatment in all stages of their lives, including pregnancy and lactation.
- Many treatments are not approved for use during pregnancy and lactation.
- Women with psoriasis have many comorbidities that should be recognized and treated.
- Women have more psoriasis (as measured by DLQI) than men, and prescribing patterns differ between genders.

What is new from this article as messages for women and their families?

- This review offers a concise overview of studies examining differences in psoriasis between men and women regarding disease burden, risk factors and treatment prescription patterns, treatment response, and adverse events.
- Topical steroids can be prescribed with a high degree of safety during pregnancy. In contrast, other topical therapies (calcineurin inhibitors and vitamin D analogs), studies on adverse effects in pregnancy are lacking, and safety data mainly stem from studies assessing effects after systemic administration.
- Safety studies on monoclonal antibodies, especially anti-TNF alpha, are inconsistent and difficult to compare. Recent data from a large population-based registry study showed that anti-TNF alpha agents that can cross the placental barrier could be associated with an increased risk for preterm birth, cesarean section, and small for gestational age.
- Postmarketing data for other biological agents such as anti-Il-17, anti-IL-23, and anti-IL-12/13 monoclonal antibodies are not yet or only partially available, and appropriate studies are now being carried out.

high-quality narrative review, scale for the quality assessment of narrative review article scale was followed. The scale for the quality assessment of narrative review article scale is currently the best-established tool for quality assessment of a manuscript based on a 6-item questionnaire.[13]

This article did not include psoriasis arthritis, pustular psoriasis, and subforms other than plaque psoriasis.

Results

Epidemiology

The mean age of onset of psoriasis is at 33 years. However, it presents at a younger age than in men than in females. In women, psoriasis usually manifests at 16 to 22 years or 55 to 60 years. In men, these 2 peaks for age at onset occur more around 30 to 39 years and 60 to 79 years.[14] This bimodal peak is associated with the 2 different subtypes of psoriasis, type I with onset before the age of 40 years (75% of cases) and type II with onset after 40 years.[4,5]

In a recent systematic review, 159 studies reporting on the prevalence of psoriasis were identified, some of which compare the prevalence of the disease in women and men.[14,15] Some studies included in this systematic review and also a newer study from Denmark with individuals of all ages demonstrated a higher prevalence of psoriasis in females,[16–18] and other studies showed the opposite, with the male population having a higher prevalence.[19,20] However, in various other studies, the prevalence of psoriasis between the sexes did not differ.[1,15,21–27] In a Danish cross-sectional study in children with autoimmune diseases, psoriasis prevalence was higher in girls than in boys.[28]

Studies reporting on the incidence of psoriasis are scarcer and mainly conducted in western or eastern Europe and North America.[14] Studies about variations in incidence rates by sex are somewhat contradictory. In some studies, the incidence was higher in women[16,29,30] and some in men.[31,32] In one population-based study from the United States, analyzing the incidence of adult-onset psoriasis between 1970 and 2000, the overall incidence of psoriasis in men was higher than in women (85.5 per 100,000 person-years in men vs 73.2 in women). The highest incidence for men was found in their seventh decade of life (115.3/100,000), for women in their sixth (90.7/100,000), in which they also have a higher incidence than men.[31] In children, one study from the United States showed a higher incidence rate in girls than in boys who are <18 years of age (43.9 vs 37.9/100,000 person-years).[32,33]

There is no robust evidence that the prevalence and incidence of psoriasis differ between men and women. Quite clearly, other factors, such as genetic predisposition and environmental factors, are more potent risk factors for the development of psoriasis.[4]

Gender-related risk factors for the development and severity of psoriasis

Genetic factors

Psoriasis is thought to be caused by the interaction of multiple genetic and environmental risk factors.[34] Its incidence is higher among first- and second-degree relatives and more concordant among monozygotic than dizygotic twins. Several genomic regions (loci) were identified in linkage studies, with PSORS1 being the most important.[34] PSORS1 is located on chromosome 6p21.3 and is an important locus for psoriasis susceptibility. PSORS1 is responsible for approximately 35% to 50% of the heritability of the disease.[35] HLA-Cw6 is located on the PSORS1 locus and is an important psoriasis susceptibility allele.[36–38] An association of HLA-Cw6 positivity with early-onset psoriasis and a more severe and unstable course was identified.[36,39]

Few studies compared the genetic differences between men and women who have psoriasis. In one study from Iceland, women who were HLA-Cw6-positive (Cw6+) had an earlier disease onset than HLA-Cw6-positive (Cw6+) men and experienced remission of psoriasis during pregnancy more frequently than HLA-Cw6-negative (Cw6–) women.[40] A small study showed a positive correlation of female sex with the Cw6+ allele and the CCHCR1+ allele (earlier *HCR1*). *CCHCR1* is a gene on the PSORS1 locus on chromosome 6p21.3. In this study, CCHCR1+ positivity was negatively correlated with disease severity.[41]

Genetic factors and polymorphisms could modify the disease course, manifestation, and treatment response in patients with psoriasis of the skin. Currently, no genetic testing or biomarkers are being used to assess these factors in clinical practice but could become relevant in the future.[42]

Other risk factors

Various studies have identified obesity as a risk factor for the development of psoriasis in both women and men. Obesity is associated with a more severe psoriasis phenotype.[43–45] Even though psoriasis and body mass index seem to correlate equally with both sexes, psoriasis, and metabolic syndrome (MetS) do not.[45] In a large population-based study in Germany (n = 3723), the probability of a psoriasis diagnosis was higher in women with MetS and body mass index ≥30 than in men. Additionally, in women with psoriasis, several cardiometabolic risk factors (waist

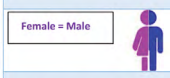
	Examples of Gender Differences	Comments	Source
	Prevalence of comorbid cardiometabolic risk factors	Compared to general population of same gender	46
	DLQI		57, 64
	Likelihood of depression		64, 65 , 66 ,
	Perceived stigmatization		67, 68
	Burden of disease		67, 68
	Treatment expectations		67, 68
	Importance of (perceived) safety for treatment choice		98
	Likelihood to receive topical treatment	At same severity	99
	Likelihood of side effects from systemic treatment		100, 102
	Disease manifestation/ morphology	No clear evidence for differences	56
	Age of onset	Two peaks, both later for males	14
	Severity (PASI)		58, 59
	Likelihood to receive phototherapy	At same severity	99
	Likelihood to receive systemic treatment		58, 60, 61
	Satisfaction with biological treatment		103
	Incidence (contradicting evidence)	Female > Male	16, 29, 30
		Female < Male	31, 32
	Prevalence (contradicting evidence)	Female > Male	17, 18, 72
		Female = Male	1, 15, 21, 22, 23, 24, 25, 26, 27
		Female < Male	19, 20
	Prevalence of comorbid MetS (contradicting evidence)	Increased in women only	46
		Female <= Male	47
	Effectiveness of systemic treatment (contradicting evidence)	Female > Male	101
		Female = Male	100
	Treatment adherence for biological treatment (contradicting evidence)	Female > Male	104
		Female < Male	103

Fig. 1. Overview of known gender differences in psoriasis.

circumference, obesity, elevated triglycerides, elevated blood glucose, diabetes mellitus, metabolic syndrome, intake of antihypertensives, and antidiabetics) were more prevalent than in women who do not have psoriasis—a reverse finding was true for men.[46]

Contrarily to this, a uniformly higher prevalence of MetS in both men and women with psoriasis was found in a large cross-sectional study (n = 10,521) in Norway.[47,48]

In the general population, cardiovascular risk factors and metabolic diseases are unevenly distributed between men and women. The mechanisms that explain sex-specific differences in these diseases are not entirely understood but investigated intensively.[49,50]

Differences in gene expression from sex chromosomes could lead to differences in cardiovascular function.[51] However, it is unclear whether and how sex influences psoriasis and cardiovascular disease. Cardiometabolic disease associated with psoriasis and the corresponding sex-specific analysis requires further investigation. It seems feasible to screen psoriasis patients and especially women specifically for cardiometabolic disease, in the short term.

In addition, smoking and alcohol consumption contribute to psoriasis severity, and the association of both factors is higher in men than in women.[45,48,52,53] These findings may be partially explained by the higher alcohol consumption and smoking rates observed in men than women.[54,55]

Clinical aspects, quality of life, and mental health

Disease severity and clinical manifestation

Psoriasis has many different clinical phenotypes.[4] No clear evidence regarding differences in psoriasis morphology between sexes exists.[56] The question of whether men have more severe psoriasis than women was first investigated in 1945,[57] and various studies have found severe forms of psoriasis to be more common in men than in women.[58,59] In a large cross-sectional in Sweden (PsoReg, n = 5438 patients with moderate-to-severe psoriasis), men had a higher median Psoriasis Area and Severity Index (PASI) at first presentation than women (7.2 vs 5.4, P < 0.001).[57] In addition, certain studies have shown that men are more likely to be prescribed systemic therapies. It has been hypothesized that the reason for this may be the difference in disease severity.[60,61]

Quality of life and mental health

Psoriasis has adverse effects on QoL, such as the impact of diabetes, ischemic heart disease, and cancer.[62] Psoriasis affects QoL to a greater extent in women than in men, despite their lower mean PASI (as measured by the Dermatology Life Quality Index [DLQI]).[57] Compared with the general population, psoriasis patients are more likely to be diagnosed with depression,[63] and female psoriasis patients are more likely to have depression than males,[64–66] which can potentially lead to a lower QoL in women who have psoriasis.[64] In a polish cross-sectional study (n = 219), the risk for depression in female psoriasis patients was significantly higher than in males.[66] Interestingly, the severity of psoriasis did not correlate with the degree of deterioration in mental health or QoL.[66] Factors that could affect QoL in psoriasis patients are the degrees of perceived stigmatization, the burden of disease, and treatment expectations, which were all higher in women.[67,68]

Identifying depression and factors leading to a deterioration in mental health or QoL in psoriasis patients, especially in women, is essential since psychiatric diseases are associated with poor treatment response, poor treatment adherence, and

Table 1.

Summary of evidence related to use of topical, conventional systemic and biologic therapies in pregnant women/women of childbearing potential

Route of administration	Drug	Systemic absorption, transplacental transfer	Maternal risk (eg, preeclampsia, gestational diabetes)	Fetal and neonate risk	References
Topical	Corticosteroids	Possible	Exist with oral use	Conflicting evidence regarding low birth weight if very high cumulative dose applied topically	108-111
	Pimecrolimus, Tacrolimus	Very low risk of systemic absorption due to large molecule size, transplacental transfer upon systemic administration possible	Not investigated upon topical administration	No direct or indirectly harming effects upon topical administration. Toxicities upon systemic administration.	112-115
	Calcipotriol/ Calcitriol	Possible	Not investigated upon topical administration	No teratogenicity in embryo-fetal studies with oral application of calcitriol in rats. Subcutaneous application in rabbits lead both to maternal toxicity and developmental toxicity at very high doses. Skeletal abnormalities associated with systemic use. Use <25–50 g/week for 3–4 weeks according to expert opinion.	118, 119
Phototherapy	Narrowband UVB	Not applicable	Folic acid deficiency	Neural tube defects secondary to folic acid deficiency	123
Systemic	Cyclosporine	Yes	Hypertension in pregnancy, gestational diabetes mellitus, preeclampsia, infection	Potential risk of low birth weight, no increased risk of congenital malformations or fetal death	124-126
	Certolizumab	Very low level in umbilical cord blood	No	No increased risk of miscarriage, congenital malformation, fetal death, risk of infection in the first year of life, no impairment of development	128-130
	Adalimumab	Yes (presumably)	No signals specific to maternal risk	Conflicting evidence regarding risk for preterm birth, small for gestational age and cesarean delivery	128,134,140-142
	Etanercept	Yes	No signals specific to maternal risk	- Conflicting evidence regarding risk for preterm birth, small for gestational age and cesarean delivery - VACTERL-association	131,135,136,140
	Infliximab	Yes	No signals specific to maternal risk	- Conflicting evidence regarding risk for preterm birth, small for gestational age and cesarean delivery - Conflicting evidence regarding risk of severely small for gestational age	132,133,140
	Ustekinumab	Yes	Very limited data No signals specific to maternal risk	- Retrospective cohort study (Wils 2021) of 29 pregnancies during ustekinumab treatment for Crohn's disease resulted in 26 (90%) live births, 2 (7%) spontaneous abortions and 1 (3%) elective termination (comparable to rates among general population).	145,146 - Prospective study ongoing (NCT02103361)
	Guselkumab	Presumably yes	Very limited data Use in pregnant women has not been studied	- 24 maternal pregnancies were reported in preauthorization studies: no safety signals in pregnancy outcomes have been observed based on limited data from the GUS clinical development program. - No effects on fertility or early embryonic development or maternal-fetal outcomes in guinea pigs. - Possibility of stillbirths and spontaneous abortions in monkeys.	152 - Prospective study ongoing (NCT02103361)
	Risankizumab	Presumably yes	Very limited data No signals specific to maternal risk	Limited data.	- Prospective study ongoing (NCT04846959)
	Tildrakizumab	Presumably yes	Very limited data No signals specific to maternal risk	No increased rate of abortion or congenital malformation. No congenital malformation in animal studies.	148,153
	Ixekizumab	Presumably yes	Very limited data No signals specific to maternal risk	Limited data, Lilly safety database: No increased rate of abortion or congenital malformation	147,149
	Secukinumab	Presumably yes	Very limited data No signals specific to maternal risk	Limited data, Novartis safety database: No increased rate of abortion or congenital malformation	148

Table extended and adapted from Yeung et al.[151]
UVB, ultraviolet B.

inferior outcomes and are an additional source of disability and suffering.[69–71] Additionally, depression is associated with an elevated risk of stroke, myocardial infarction, and cardiovascular death in patients with psoriasis.[72]

Effects of female sex hormones on the skin and psoriasis

Female sex hormones, notably estrogen, can have beneficial effects on skin aging, water-binding capacity, and wound healing.[73–76] For example, transdermal estrogen application in perimenopausal women increases skin water-holding capacity potentially by improving stratum corneum barrier function.[77] Beyond that, female sex hormones also affect the disease manifestation and severity of psoriasis. High estrogen levels, as seen in pregnancy, and increased estrogen to progesterone-ratios correlate with improvement of psoriasis; progesterone alone, however, does not affect psoriasis.[78] Several studies reported an improvement of psoriasis during pregnancy in about 50% of psoriasis patients, whereas approximately one-quarter experienced worsening during pregnancy, and one-quarter reported no effect.[78–80] So far, it is unknown, whether the improvement of psoriasis is driven by increased estrogen levels alone or in combination with elevated cortisol levels.[81]

Sex hormones, however, influence the cytokine imbalances in psoriasis patients. Low estrogen levels are associated with predominantly Th1-cell immune responses and proinflammatory cytokines, whereas high levels of estrogen promote upregulation of Th2 cell-dependent cytokines.[82] Accordingly, estrogens are negative regulators of tumor necrosis factor (TNF), which plays a crucial role in psoriasis pathogenesis. Its production is also increased during the luteal phase of the menstrual cycle when low estrogen levels. This explains the sometimes-observed improvement of psoriasis during the menstrual cycles.[82,83]

Pregnancy, pregnancy outcomes, and fertility

Several studies address whether chronic inflammation as in psoriasis- and psoriasis-related comorbidities increase the risk of complications during pregnancy or not.[79] In a systematic review of observational studies assessing adverse pregnancy outcomes in psoriasis, no clear evidence of increased adverse effects could be found in a total of 4756 pregnancies, and no clear stratification of results between mild and moderate/severe disease was made in all included studies.[84] In a population-based cohort study (total: 8097 births in 6103 women with psoriasis and 964 births in 753 women with psoriasis arthritis), an increased risk for hypertension, preeclampsia, gestational diabetes, elective, and emergency cesarean delivery was found mainly in women with severe psoriasis.[85] In a longitudinal study (Psoriasis Longitudinal Assessment and Registry) assessing pregnancy outcomes (women with moderate-to-severe psoriasis), 298 pregnancies of 220 women resulted in 244 (81.9%) live births.[79] This study's pregnancy-related adverse events (congenital disabilities, spontaneous abortion, neonatal problems) were comparable to the general US population. Outcomes in women receiving biologics were like those receiving conventional systemic therapies. However, the annual fertility rate in the study population (women with psoriasis and of childbearing age) was lower than in the general US population in 2018 (18.9 pregnancies vs 59.1 pregnancies in 1000 women of childbearing age).[79] Similarly, in the Spanish Registry of Systemic Treatments in Psoriasis (Biobadaderm), the fertility rate among women of childbearing age with moderate-to-severe psoriasis was lower than that of women of the same age in the general Spanish population.[86]

When counseling psoriasis patients with a desire to have children, one must keep in mind that most studies investigating pregnancy outcomes and fertility were conducted in patients with moderate-to-severe psoriasis. Data regarding the impact of psoriasis on women's fertility is controversial, especially since most studies do not discriminate between mild- and moderate-to-severe psoriasis. Although psoriasis probably does not directly impact fertility, a systemic inflammatory state as in psoriasis could be responsible for the overall reduction of pregnancies, as observed in the Psoriasis Longitudinal Assessment and Registry and Spanish Registry of Systemic Treatments in Psoriasis (Biobadaderm). Compared with women without psoriasis, women with psoriasis have an elevated risk of comorbidities (eg, metabolic syndrome, diabetes, cardiovascular disease), which could also affect their fertility.[87,88] In a recent Danish cross-sectional study, women with psoriasis had higher odds for having other immune-mediated diseases such as spondylarthritis, Crohn's disease, and psoriatic arthritis.[89]

In autoimmune disorders, a dysregulated balance of Th17 and regulatory T cells is characteristic and an increase of Th1 and Th17 cells in the pathogenesis of psoriasis is well established.[90,91] This immune dysregulation could affect pregnancy outcomes or fertility. In psoriasis, rheumatoid arthritis, and inflammatory bowel disease, proinflammatory cytokines are elevated in the mother's serum and umbilical cord.[92] In particular, the cytokine milieu is critical for successful embryo implantation. Proinflammatory cytokines produced by Th1 cells are embryotoxic and can complicate fetoplacental development (Fig. 1). To prevent fetal rejection, the immune system changes during pregnancy; hormonal changes lead to a reduction in the Th1 cell-dependent immune response and enhance the Th2-dependent immune response and increase the regulatory T-cell subset, which might prevent cell-mediated rejection of the fetus.[91] Subsequently, this reduction in proinflammatory Th1 and Th17 cytokines play a role in improving psoriasis during pregnancy.[93,94]

Treatment, treatment response, side effects, and discontinuation

Various treatment options are available for the management of psoriasis (Table 1). These can be selected based on disease severity, comorbidities, patient preferences, and expectancies, including topical treatments, phototherapy, photochemotherapy, and systemic agents.[95,96] Usually, the severity of psoriasis is divided into 2 categories: mild psoriasis and moderate-to-severe psoriasis. Mild disease usually requires only topical treatment, whereas additional phototherapy or systemic therapy may be necessary for moderate-to-severe disease.[96] Besides severity, the location of the skin lesions (eg, on hands and feet, on face) and the presence or absence of joint involvement (psoriasis arthritis) play a significant role in the treatment selection. New systemic treatments are very efficacious; however, the cost is also high. Therefore, conventional therapies such as phototherapy and methotrexate still play an important role when treating patients with psoriasis.[97] In principle, all forms of therapy are available independent of sex. However, depending on sex, differences in prescribing patterns were identified in a survey of 1000 dermatologists in the United States. The treatment decision in women was more driven by the safety of the treatment; therefore, women received medications with a lower perceived risk for side effects than men.[98]

Many studies have found differences in the prescription patterns of psoriasis treatments. In a retrospective study in Sweden (n = 326, 51% men), women were less likely to receive phototherapy. They were more likely to receive topical treatments for home administration than men with the same psoriasis disease severity.[99]

In a Swedish population-based cohort study (data from the nationwide quality registry of psoriasis patients, n = 2294, 58.9% men), men were more severely affected by psoriasis and more likely to receive systemic treatment.[58] Contrarily to this, in a Spanish cohort study (n = 2881; 58.3% men), women had a 33% higher chance of being prescribed a modern therapeutic

agent.[100] In a 2-country, multicenter, prospective, noninterventional registry study (n = 5346, 67.3% male) evaluating gender differences regarding systemic antipsoriatic treatment, women had a higher PASI response and were more likely to achieve a DLQI reduction of ≥4.[101] In a Spanish registry study, however, treatment effectiveness of systemic treatment was similar in women and men.[100] Regarding side effects, women were more likely to experience acute infections during treatment with biologic drugs in an Italian study (n = 167, 63.4% men) and more side effects in a Spanish study (n = 2881, 58.3% men) when treated with a systemic agent.[100,102]

Prospective data from the Dutch psoriasis registry (n = 315, 59.7% men) showed that women were less satisfied with biological treatment regarding global satisfaction and side effects and treatment discontinuation was higher in women,[103] whereas, in an open comparator study from the United Kingdom (n = 201, 44.2% men), treatment adherence was higher in women.[104]

Treatment and safety concerns during pregnancy and quality of evidence of reporting studies

Even though psoriasis improves in approximately 50% of women during pregnancy, effective treatment is needed, especially for moderate-to-severe psoriasis. In the postpartum period, psoriasis usually returns to baseline before conception.[78,80] In usual psoriasis patient care, pregnant psoriasis patients should be treated according to their subjective and objective disease severity. However, various topical and systemic treatments should be avoided due to patient, fetal or neonate risk.[105] Since pregnant women are usually excluded from clinical trials, and many discontinue treatment during pregnancy, data on treatment are limited.

Topical treatments

Emollients are safe to use during pregnancy and lactation.[106,107] In mild and moderate disease, topical treatment with corticosteroids is possible. However, topical steroids can have systemic effects and side effects in pregnancy.[108,109] Several studies have addressed the impact of topical steroids on the fetus and neonate, and data are conflicting.

In a systematic review, a very high cumulatively applied amount of topical corticosteroids during pregnancy was associated with low birth weight.[110] However, a recent large-scale, retrospective cohort study from Denmark evaluating 60,498 pregnancies in which topical corticosteroids had been used has refuted this assumption.[111] Therefore, potent topical corticosteroids are probably also safe during pregnancy.

Topical use of calcineurin inhibitors (TCI), namely pimecrolimus and tacrolimus, cannot be generally recommended in pregnancy. TCI are very large molecules, and therefore the penetration in the skin and systemic absorption is not very likely if the skin barrier is intact. Nonetheless, studies in humans on adverse pregnancy outcomes after use of TCI do not exist, and toxicity studies stem from systemic application mainly in organ transplant patients.[112–115] The use on small surfaces and not directly on the mammilla during breastfeeding is probably safe.[3,116]

Topical vitamin D analogs (calcitriol, calcipotriol) should be used with caution in pregnancy and only if no alternatives exist.[3,117] In animal studies with rabbits, maternal and developmental toxicity were observed upon subcutaneous administration at high doses, and skeletal abnormalities were associated with systemic use.[118,119] Data with humans are not available. Coal tar and anthralin should be avoided due to lack of data and mutagenic/carcinogenic potential in animal studies. Tazarotene should be avoided during pregnancy and lactation due to its teratogenic potential.[107,117,120,121]

In general, the administration of topical drugs is associated with potentially harmful consequences for the unborn child through systemic absorption and transplacental transfer.

For many topical agents, no studies or only animal studies are available regarding their effect upon topical use in pregnancy. Treatment recommendations are primarily based on studies in which these drugs were used orally.

Phototherapy

In moderate-to-severe disease and insufficient topical treatments, phototherapy can be used during pregnancy but some safety concerns exist.[122,123]

Narrowband ultraviolet B exposure but not ultraviolet A exposure degrades folate in a dose-dependent manner and can therefore only be recommended in pregnancy if an adequate folic acid supply is ensured. Even in women of childbearing age, folic acid substitution during phototherapy with narrowband ultraviolet B should be considered to prevent congenital disabilities in unplanned pregnancies.[123]

Systemic treatments

Most traditional systemic treatments (methotrexate, retinoids) are contraindicated in pregnancy and women wishing to conceive due to high risks of teratogenicity. Women wanting to conceive should stop acitretin at least 3 years before conception and methotrexate and fumarates at least 6 months before conception.[107]

Cyclosporine can be prescribed with reservations. Reproductive toxicity has been demonstrated in animal studies in rats and rabbits. However, data on the use of cyclosporine in pregnant women with psoriasis are limited. The data of cyclosporine mainly stem from experience in transplantation medicine. Following transplantation, pregnant women treated with cyclosporine are at increased risk for preterm delivery.[124–126] There are a limited number of observations of children up to 7 years of age who were exposed to cyclosporine in utero. Renal function and blood pressure in these children were normal; however, a risk of prematurity and low birth weight was also associated.[117,120]

Concerning the use of biological drugs during pregnancy, postauthorization data are available for adalimumab, certolizumab pegol, etanercept, and infliximab. Only limited data exist for other biologics licensed for the use in psoriasis in women of childbearing age or are currently being collected in prospective studies and registries.[127]

When clinically needed, certolizumab pegol can be used during pregnancy and lactation in women with moderate-to-severe psoriasis.[128] Certolizumab pegol is a pegylated Fc-free anti-TNF-α Fab fragment, which does not actively cross the placental barrier during pregnancy and shows no to minimal transfer from plasma to breast milk during lactation.[129,130] In January 2018, European Medicines Agency approved a label change making it the first anti-TNF-α and first biological for potential use in pregnancy and lactation. Unlike certolizumab pegol, other anti-TNF-α monoclonal antibodies were found in umbilical cord blood in varying concentrations.[131–133]

Various studies, especially from gastroenterology and rheumatology, have investigated whether anti-TNF-α monoclonal antibodies harm pregnancy outcomes ranging from single case reports and small case series[131–136] of pregnancies during infliximab or etanercept treatment to extensive retrospective cohort studies[137] and prospective (registry) studies[138,139] and observational studies.[140–142] The generalizability of results is limited due to heterogeneous study designs and variable outcomes and endpoints. A meta-analysis by Komaki comparing 13 different studies showed wide confidence intervals, especially for adverse event outcomes, which reduces the power of these safety studies.[143] Nevertheless,

this meta-analysis shows an increased risk for preterm birth (relative risk: 1.36), comparable to the one estimated in a recent registry study from Denmark (relative risk: 1.56).[140] In this study from Denmark comparing >1000 births of anti-TNF-α monoclonal antibody exposed infants with 9399 infants to women treated with nonbiologic systemic treatments (for inflammatory bowel diseases, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis), anti-TNF-α monoclonal antibody exposure was also associated with increased risk for emergency cesarean section and small for gestational age.

Overall, anti-TNF-α drugs, except certolizumab pegol, are transmitted diaplacentally and detected weeks after birth. Adverse outcomes are not impossible and could also result from the increased risk of infection associated with anti-TNF-α therapy during pregnancy, which is also an independent risk for preterm delivery.[139,140,144]

Postmarketing data are lacking for newer drugs such as IL-17 monoclonal antibodies and IL-23 p19 monoclonal antibodies. There are very few cases of unplanned pregnancies in premarketing studies, most of which resulted in pregnancy discontinuation. In animal studies, mainly conducted on monkeys, few safety signals concerning fetal risk were observed. More data are now being collected in several prospective registry studies.

In a cohort study in patients with Crohn's disease, 29 pregnancies during ustekinumab treatment resulted in 26 (90%) live births, 2 (7%) spontaneous abortions, and 1 (3%) elective termination, which is comparable with rates among the general population.[145,146] A few reports show no increased rate of abortion or congenital malformation for exposure to ixekizumab, secukinumab, or tildrakizumab during premarketing clinical trials.[147–149] Due to animal studies in cynomolgus monkeys showing a dose-dependent increased risk for abortion and embryo-fetal death, apremilast is contraindicated during pregnancy.

There are many safe treatment options for pregnant and breastfeeding women with psoriasis, including topical therapies, light therapy, and highly effective systemic therapies such as certolizumab pegol.[150] Clinical trials on the safety of risankizumab (NCT04846959), tildrakizumab (NCT03992729), ustekinumab, and guselkumab (NCT02103361) in pregnancy are ongoing and will give us more information on the safety of these drugs in pregnancy.[151–153]

Conclusion

Gender medicine is an essential and new field of research. For decades, pregnant women have been automatically excluded from clinical trials. Using psoriasis as an example, we have shown in this review that women have more psoriasis than men do, respond differently to treatments, and that differences in prescribing patterns exist. Women with psoriasis have a lower socioeconomic status and higher use of health resources, including prescription analgesics. Regarding the treatment of women of childbearing age, many safe options exist. However, safety concerns exist for novel, biological therapies during pregnancy and lactation. Today, postmarketing studies are lacking for many of these drugs, and pregnancy-specific registries are needed to characterize the effect of psoriasis and its treatment more fully on birth outcomes.

In the future, we believe that therapies will be tailored, for example, the biologic drug may only be selected after a more precise determination of the cytokine profile or, for example, metabolic markers. In this situation, it needs to be explored whether there are differences in disease phenotype between women and men and how this might influence therapy choices. Furthermore, there is a need to examine whether different therapies result in different responses and, if so, whether specific treatments are superior for women than for men or vice versa. These questions could be addressed in prospective registries, and appropriate guidelines could result.

Author contributions

- CG: Conception and design, acquisition/analysis, and interpretation, drafting of the article, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- CS, NM: Conception and design, drafting of the article, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- JTM, LVM: Conception and design, data interpretation, critical revision for important intellectual content, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- JTM: Conception and design, acquisition/analysis, and data interpretation, drafting of the article, critical revision for important intellectual content, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of interest

- CG: served as advisor and participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Celgene, Eli Lilly, Novartis; received a research grant from EAACI (European Academy of Allergy and Clinical Immunology) to perform research outside of the submitted work at the Department of Dermatology of Charité—Universitätsmedizin, Berlin.
- CS, NM: None.
- LVM: served as advisor or received speaking fees or participated in clinical trials sponsored by Amgen, BMS, Celgene, Eli Lilly, MSD, Novartis, Pierre Fabre, Roche, Sanofi.
- LVM: Conception and design, data interpretation, critical revision for important intellectual content, final approval, agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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