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Dermatologic Therapy
Volume 2025, Article ID 6670747, 9 pages
https://doi.org/10.1155/dth/6670747

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Review Article

Sex Differences in Epidemiology, Mechanisms, and Management of Atopic Dermatitis

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Received 27 February 2025; Revised 19 September 2025; Accepted 20 September 2025

Academic Editor: Sebastian Yu

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Sex differences in disease are of increasing importance. They depend primarily on the hormonal status, which can influence immune responses and metabolic pathways, as well as response to treatments. Sex differences have been described for both innate and adaptive immune cells, and sex hormones are important regulators of Th2 immunity. Atopic dermatitis (AD) is a common inflammatory skin disorder with a chronic and relapsing course. AD prevalence rates have increased over recent decades, especially in urbanized and industrialized regions. Approximately 5%–20% of children and 5%–8% of adults suffer from AD. AD is more prevalent in adolescent females and females of child-bearing age, who also suffer from more severe and persistent AD symptoms compared to males. Menstrual periods and pregnancy frequently lead to a worsening of AD symptoms. Indeed, estrogens potentiate, while androgens reduce Th2 immune response and increase T regulatory cell activity. Sex hormones also affect the skin barrier function. Monoclonal antibodies against Th2 cytokines are more effective in females. Major concerns about treatment arise in pregnant females and those planning a pregnancy. Only cyclosporine and azathioprine (off-label) are suggested in pregnancy when the benefits exceed the potential side effects, but they are both contraindicated during breastfeeding. Methotrexate and systemic corticosteroids are contraindicated during pregnancy and lactation. Some reports have described safe and effective use of dupilumab during pregnancy, but evidence remains limited; therefore, it is not recommended during pregnancy because of the scarce data on safety. There is no data about tralokinumab and lebrikizumab use during pregnancy, so their use is preventively avoided. Abrocitinib, baricitinib, and upadacitinib are contraindicated during pregnancy and breastfeeding, and some teratogenic effects have been described in animal models.

1. Introduction

Atopic dermatitis (AD) is a chronic, inflammatory skin disease with a complex pathogenesis mostly related to defects in the skin barrier, skin hyperreactivity to inflammatory signals as well as a tendency to develop type 2 immune responses. Although considered a childhood disease, it is now evident that AD is common also in adulthood and even in the elderly population [1–5]. In classical presentation, AD affects the face and neck area as well as the flexural areas including the neck, cubital and popliteal fossae, wrists, and ankles. In the acute phases, AD presents with erythema, edema, vesicles, oozing, crusting, and excoriation. Erythema, desquamation, and lichenification characterize chronic lesions. Itch is a dominant symptom and is the major responsible for disease burden [1, 2]. Scratching promotes skin inflammation and epidermal barrier deterioration and may also favor cutaneous infections, such as impetigo and herpes virus infections, as well as extra-cutaneous infections. Clinical severity ranges from mild to moderate-to-severe disease, with an intermittent or persistent disease course [1, 2]. Worsening in physical, emotional, and social functioning is common also in moderate forms [1]. Diagnosis of AD is based on clinical findings, including history, morphology and distribution of lesions, and associated signs and symptoms [3, 4]. AD frequently presents with other atopic diseases such as asthma, allergic rhinitis and conjunctivitis, and food allergies. Growing evidence also indicates an association of AD with neuropsychiatric disorders, autoimmune diseases, and perhaps cardiovascular diseases [5–10].

Sex differences have been reported in patients with AD including prevalence, disease course, severity, and psychosocial impact. Sex differences depend nearly on hormonal status and may involve functions of the skin, immune responses, and metabolic pathways, and have to do also with indications and responses to treatments [11–14]. Therefore, it is important to consider a sex perspective in the treatment of AD including her willingness to procreate. This is a narrative review highlighting the gender differences in epidemiology, clinical features, disease mechanisms, and challenges in the management of AD in female patients.

2. Methods

This is a narrative review. The selection of articles was based on relevance to the topic, regardless of study type (including randomized controlled trials, observational studies, and reviews). A flowchart according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines is reported as Figure 1. Electronic searches were performed on the PubMed database using "(AD) AND (sex and gender differences)" as search terms. Articles published between January 2000 and December 2024 was included. A total of 346 papers were first evaluated, and of these, 288 were estimated to be relevant. At the end, only 51 articles were included in the current narrative review, as they were considered appropriate, and they were the only ones that closely reflected the topic of the study. In fact, some articles did not have AD as a topic, and others had AD but did not discuss sex differences. Two investigators (MM and MDG) extracted data by using an extraction form. Two authors (PG and GG) were consulted to resolve any disagreements. Articles were screened by title and abstract, and those deemed relevant were reviewed in full text and selected or rejected based on the inclusion and exclusion criteria. The following age groups were considered: preschoolers (< 6 years), school-aged children (6–12 years), adolescents (13–17 years), adults (18–65 years), and elderly (> 65 years).

2.1. Prevalence of AD. The prevalence of AD is about 16.0% in preschoolers, 9.7% in school-aged children and 8.6% in adolescents and is slightly higher in males (8.7%) than females (5.6%) during childhood [15, 16]. However, this prevalence tends to equalize as children grow; and after puberty the sexual difference is reversed because the immune responses of patients are remarkably influenced by sex hormones [15]. A prevalence of 6.0% and 8.0% in Europe and in the USA, and 5.7% and 8.1% in Japan for males and females after puberty has been reported, respectively [16]. Approximately 5%–8% of adults are affected by AD, with 66% having persistent AD from childhood, and one-third experiencing adult-onset AD. Severe AD is more frequent in adults. In adults, a female predominance has been repeatedly detected, with a prevalence of 6.4% for females and 4.4% in males, and is particularly higher among women aged 30–49 years, whereas AD predominates in males among elderly patients [4, 15]. Considering adult patients, the prevalence of AD was particularly higher among females in Latin countries, Saudi Arabia, Egypt, Malaysia, Russia and even higher in Turkey (30.9% in females vs. 12.4% in males) [15]. In contrast, AD prevalence has been reported higher in males in Taiwan and the United Arab Emirates. Also, chronic hand eczema, including AD hand eczema, is much more common in females than males [17, 18]. Interestingly enough, asthma is also more common in young males than young females but then more prevalent in adult females than adult males, and severity tends to fluctuate with critical phases of hormonal changes [19].

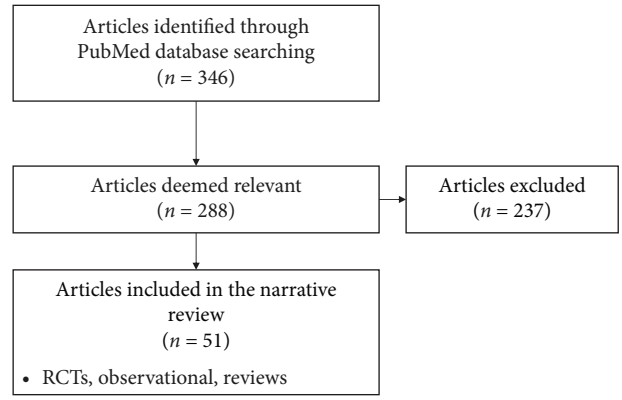


Figure 1: Flowchart according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

2.2. Disease Severity and Symptoms. Preschooler (< 6 years) males affected with AD have shown more severe symptoms compared to females during childhood, school-aged (6–12 years) males and females have a similar symptom severity, while adolescent (13–18 years) females have more persistent symptoms and higher severity of AD, especially during puberty [13–15]. Changes in the levels of estrogen and progesterone during the menstrual cycle correlate with worsening of AD during the luteal phase, with improvement during or after menstruation [13, 20]. More than one-third (32%–47%) of females have noticed deterioration of AD related to the menstrual cycle in several cross-sectional studies [20–25]. 64.5% of these patients experience mild worsening, and 64.0% of females reported that the deterioration in AD symptoms appeared 10 days before menstruation [26]. A French survey reported exacerbations of AD before (50.0%) and during (48.3%) menstruation [27]. In a prospective longitudinal study, women with moderate-to-severe AD experienced significant exacerbation in disease severity and itch and quality of life deterioration in the premenstrual phase compared to the menstrual and the postmenstrual period. Patients with mild AD or psoriasis did not manifest the same variation of symptoms in relation to the menstrual phase [22]. The deterioration of AD during this period might be due to the dual effects of estrogen and progesterone on Th2 activity and skin barrier [20]. AD worsens also during pregnancy in 52%–61% of cases [23, 25, 28, 29].

No significant sex differences emerged for sleep disturbance and prevalence of alopecia areata in patients affected by AD [6, 7]. Concerning metabolic comorbidities,

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the proportion of type 2 diabetes, metabolic syndrome, and hypercholesterolemia is similar between males and females, whereas hypertriglyceridemia and hypertension are more frequent in males than in females [30, 31].

Sex differences in the psychosocial impact among patients with AD have also been described. Females with AD show greater psychosocial effects compared to males, especially during adolescence. Adolescent females are more ashamed, upset and sad, and reported problems at school and age because of AD, compared to males [32–34]. In addition, school-aged children have more delayed sleep onset times and increased daytime sleepiness, particularly for females [32–34]. This difference may be due to differences in symptom severity, to societal factors, to personal body image, or to a combination of these and other elements. Adult females affected by AD are more likely to report anxiety and depression, sleep disturbances, insomnia, and fatigue, exacerbated when the AD is in the active phase. A Swedish population study (BAMSE study) reported 26.1% of sleep disturbance in adult females with AD, compared to 11.1% in adult males, when controlled for disease severity [34].

2.3. Hormonal Status and Disease Mechanisms. AD develops from skin barrier defects as well as a tendency to develop type 2 immune responses, with genetic predisposition playing a crucial role [1, 2, 5, 35, 36]. In addition, epidermal hyperreactivity to inflammatory signals contributes to disease development and perpetuation [37]. Sex hormones and X-encoded genes influence both innate and adaptive immune responses, and autoimmune diseases have a different prevalence in males and females [11, 12]. Sex hormones seem to influence also skin immunity [13, 38]. A central role for type 2 innate lymphoid cells (ILC2s) in shaping sexual immune dimorphism within the skin has been described in mouse models. In detail, negative regulation of ILC2s by androgens leads to reduced dendritic cell accumulation and activation in males, along with decreased tissue immunity. These findings reveal a role for the androgen-ILC2-dendritic cell axis in controlling sexual immune dimorphism, with a role of sex hormones also influencing the microbiota [39]. In addition, sex hormones and microbiota are modulators of tissue immunity, leading to an increased T cell response in females compared to males and a consequently increased risk of developing inflammatory diseases, such as AD [38]. Estrogens stimulate Th2 immune responses and T regulatory cell function and downregulates Th1 and Th17 immune responses [20, 38]. Instead, androgens, such as testosterone or dihydrotestosterone, support Th1 immune response and T regulatory cells while downregulating Th2 and Th17 responses [12, 20, 38]. Age is a key environmental factor that influences sex differences. Androgens are elevated in males and females during perinatal development and in males during adolescence. Estrogen and progesterone levels fluctuate throughout life span in males and females, with some concentrations changes particularly in females during puberty, pregnancy and menopause [20]. These effects of increased levels of estrogens and progesterone are linked to a stronger Th2 response with consequently higher inflammation during menstrual cycle and pregnancy (Figure 2). Skewness towards a Th2 response enhances a humoral response, leading to higher production of IgE [24, 26, 28]. Progesterone indeed promotes Th2 activity and suppresses Th1 cells [20]. In order to discover sex-specific biomarkers that can be used to differentiate between lesional and nonlesional skin in AD patients, genes involved in AD in males and females have been identified using transcriptomic dataset. The transcriptomic datasets have been developed by applying machine learning algorithms. Male-specific and female-specific gene signatures have been detected in preliminary studies [40], indicating that there are different molecular mechanisms involved in AD in males and females. Sex hormones also have a role on the skin barrier [20]. In adults, skin hydration is slightly higher in females than in males, and basal transepidermal water loss is significantly higher in males than females [20]. These alterations in skin barrier might explain why AD is more common in elderly males than females. The effects of the skin hormones on the skin barrier in humans are complex and sometimes contradictory, depending on the animal model investigated. In general, in humans it appears that the epidermal permeability barrier is impaired by androgens and progesterone and is restored by estradiol [20]. Estradiol, however, may also worsen the progesterone-induced barrier impairment. In the luteal phase, when progesterone and estrogen are both highly secreted, the skin barrier is damaged [20]. Finally, estradiol and progesterone induce the secretion of Th2-related cytokines IL-4, IL-13, and IL-31, which are the master inducers of itch sensation. Estrogens can also act on mast cells and promote the release of histamines, which act as strong pruritogens [20].

2.4. Treatment of AD. In general, there are significant sex differences in the pharmacological response to treatment [41], and the evidence for the management of AD in women of child-bearing age is limited [42, 43]. It is very important to focus on sex when considering the treatment of patients with AD and asking the woman about the willingness to procreate [44–47]. Topical corticosteroids and topical calcineurin are the most used therapies for mild diseases. Among systemic treatments, there is no different efficacy with the use of antihistamines, cyclosporine, and phototherapy between males and females. Methotrexate is more prescribed in males than females [45, 46]. There is evidence that Th2-targeting biologic treatments, such as dupilumab, but also tralokinumab and lebrikizumab, are more effective in females than in males because of the more prominent Th2 response in females [48, 49]. Adult females treated with dupilumab are 3.58 times more likely to achieve EASI-75 compared to males [48]. In pediatric patients the results are different, with females and males responding similarly to dupilumab [32, 50]. Dupilumab treatment shows significant efficacy in improving AD in patients aged 80 years and above with a high level of safety. However, differences between the two sexes have not been investigated [51].

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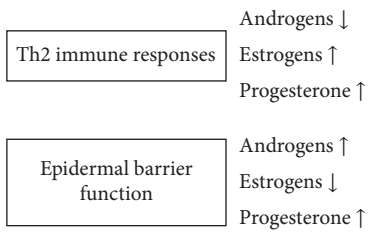


FIGURE 2: Simplified representation of the influence of sex hormones on the pathogenesis of atopic dermatitis.

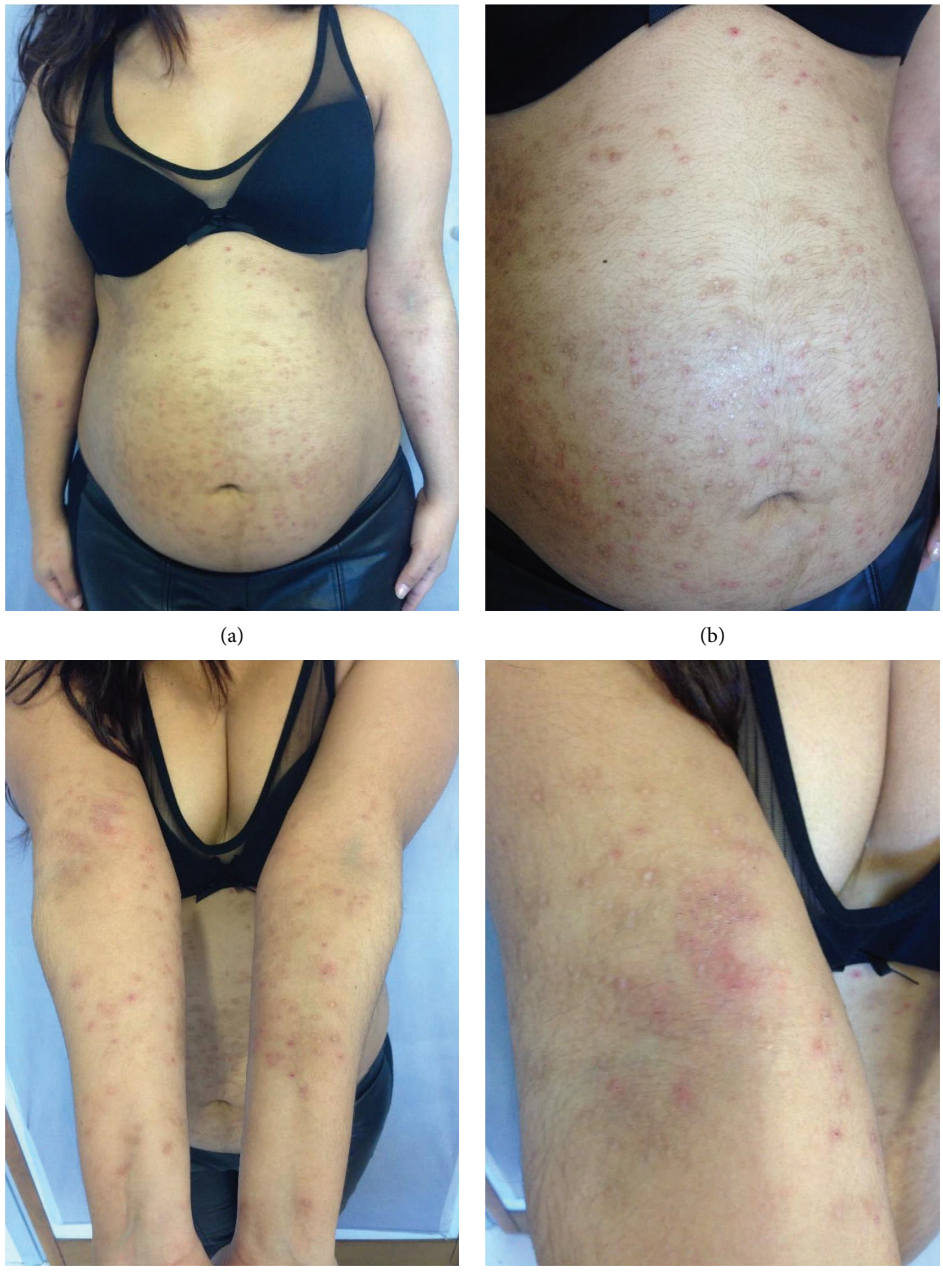
Females with moderate AD and moderate impact on quality of life are undertreated compared to males [42, 52]. It is possible that pregnancy and lactation have an influence on this undertreatment. Indeed, a cross-sectional study based on individual-level data obtained from the longitudinal population-based birth cohort BAMSE project showed that a larger proportion of men (39.0%) compared to women (29.1%) were dispensed topical corticosteroids [34]. There were no differences in the prescription of emollients. About systemic corticosteroids, women retrieved more prescriptions than men (2.29 vs. 1.30), because females may have multiple comorbidities and also be eligible for systemic corticosteroids, such as asthma and allergic rhinitis [52].

2.5. Adverse Events (AEs) From Systemic Treatments. Female sex is an independent factor for increased risk of AEs in pharmacology in relation to differences in drug pharmacokinetics and pharmacodynamics but also other biological factors and variations in immune responses [41, 53–55]. Some studies indicate that immune-mediated inflammatory diseases may also influence fertility [56–59]. Sex-specific pharmacokinetics and pharmacodynamics with a lower body weight and lean fat mass ratio in females, leading to a different distribution in tissue and consequently a different drug concentration. Furthermore, the majority of drugs for AD are not body weight adjusted, with a possible increased drug toxicity in females. Finally, the different hormonal profile, the different expression of drug-metabolizing enzymes, and a higher likelihood of multidrug use in females, can justify these sex differences. The higher rate of AEs in female patients should be taken into consideration when evaluating results in clinical trials. Females reported higher rates of cutaneous AEs, such as itching, stinging, burning, and irritation, especially with the use of topical treatments. This could be related to differences in the skin barrier function, because females have thinner skin and different lipid composition, with an increased sensitivity to topicals. Males have shown a higher susceptibility to bacterial infections, particularly due to *Staphylococcus aureus*, potentially due to differences in skin microbiome. In general, females reported progress of weight gain, hypertension, mood changes, injection site reactions, and flu-like symptoms, while males reported fewer but more serious AEs, such as increased infection risk [55].

2.6. Treatment of AD During Pregnancy and Lactation. AD is frequently observed during pregnancy [42, 60] (Figure 3). AD may either worsen or be reactivated in patients with a past history of AD or may occur in women with no AD history. This latter condition is known as atopic eruption of pregnancy (AEP). AEP typically occurs during the first trimester whereas pre-existing AD more frequently worsens during the second or third trimester of pregnancy. Almost 80% of women affected by AEP have no previous history of AD, whereas 20% of patients have chronic AD and experience a worsening of the disease [29]. In particular, 14% experienced a mild degree, 57% a moderate degree, and a 29% severe degree of AD deterioration during pregnancy [23, 29]. Pathogenesis seems to be reached in the shift toward a Th2 response that physiologically occurs in this period to facilitate a successful pregnancy [20, 23].

According to guidelines and recommendations on the treatment of moderate-to-severe AD, there are a few treatments that could be recommended during pregnancy [44–47, 61–63]. First-line treatments for AD during pregnancy are topical treatments. They are considered in mild forms, with emollients, low-to-medium potency topical corticosteroids, and/or topical calcineurin inhibitors such as tacrolimus and pimecrolimus [29]. Topical calcineurin inhibitors are non-steroidal and nonatrophogenic treatments and are suitable for the face, neck and flexural areas. However, their use in pregnancy remains off-label, although their absorption is minimal, and there is no evidence that they can be embryotoxic if used for limited periods in small areas. They are considered when topical corticosteroids are not effective or contraindicated (skin atrophy, striae rubrae), when AD is localized and when used in short courses [46]. Because of safety concerns, a reduced use of topical agents during pregnancy has been observed [29]. In refractory cases, narrow-band UVB phototherapy is an option, but the possibility to develop melasma needs to be considered. Oral antihistamines are considered safe and are an option to treat itch, in particular loratadine for the broad experience with this drug during pregnancy. During breastfeeding, guidelines suggest prednisolone only as short-term rescue therapy for acute flares [61–63]. Second- and third-line treatments are recommended in pregnant women with AD who are inadequately controlled with first-line treatments. Concerning conventional systemic treatments, only cyclosporine may be used off-label in severe forms, when the benefits exceed the potential side effects. However, an increased rate of premature births and lower birth weights has been reported with cyclosporine [64–68]. Methotrexate is contraindicated because of the high risk of teratogenicity. In parents with AD planning to have a child, guidelines recommend stopping methotrexate at least 3 months before conception. Azathioprine use during pregnancy should be avoided, as there are better options but may be used off-label at 50% dosage in the absence of other alternatives, and only as continuation of treatment in women already receiving this treatment at the time of conception [45]. Cyclosporine,

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(a) (b) (c) (d)

Figure 3: A 32-year-old pregnant female patient affected by moderate-to-severe atopic dermatitis.

azathioprine, and methotrexate are transferred into breast milk; therefore, their use is contraindicated during breastfeeding [67]. Systemic corticosteroids, such as prednisone, should be avoided as they are associated with an increased risk of fetal complications, but may be used for a short course in severe cases. The use of dupilumab during pregnancy has been reported in case reports and case series, but evidence and data remain limited [65, 69]. In a nationwide US study on 3563 pregnant women with AD, 2% of these used dupilumab during 180 days before being aware of pregnancy, 0.7% during the first, 0.3% during the second, and 0.3% during the third trimester [65]. A systematic review including 68 patients undergoing 69 pregnancies showing significant clinical efficacy and no adverse delivery or fetal outcomes. Dupilumab therapy was given continuously during the pregnancy in 22.2% of patients, while in 77.8% it was administered intermittently. Forty-nine patients were on dupilumab treatment before pregnancy, and 4 started during their pregnancies [70]. Two systematic reviews and meta-analysis conducted on pregnant women with AD also suggest that dupilumab is probably safe during pregnancy and breastfeeding [69, 71]. These data found an acceptable risk for pregnant women and their newborns, with no significant increased risk of spontaneous abortion or congenital defects [69, 71]. In addition, more recent data on 293 women exposed to dupilumab during pregnancy found

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Table 1: Recommendations for the treatment of atopic dermatitis during pregnancy, based on the European guidelines (EuroGuiDerm) on atopic eczema [44–46].

Treatment	Recommendation	Strength of recommendation
Emollients	Recommended	Strong
Topical corticosteroids (class II or III)	Recommended	Strong
Topical calcineurin inhibitors	Suggested	Conditional
Phototherapy (narrow-band UVB)	Recommended	Strong
Oral antihistamines	Can be used	Conditional
Cyclosporine	Suggested	Conditional
Azathioprine	Suggested	Weak
Methotrexate	Contraindicated	Strong
Systemic corticosteroids	Short-term use only	Conditional
Dupilumab	No recommendation (limited data)	Conditional
Tralokinumab/lebrikizumab	No recommendation (limited data)	Conditional
JAK inhibitors	Recommended against	Strong

Table 2: Major distinguishing characteristics of atopic dermatitis (AD) in female gender.

• AD prevalence is slightly higher in males than females during childhood; it is similar in adolescents; is higher in adult females • Males with AD have shown more severe symptoms than females during childhood • Adolescent females have more severe persistent symptoms, especially during puberty
• Adult females affected by AD are more likely to report anxiety and depression, sleep disturbances, insomnia and fatigue
• During menstrual cycle and pregnancy, a stronger Th2 response, with AD worsening in many females • AD and atopic eruption of pregnancy are the most frequently observed dermatosis during pregnancy • Th2 targeting biologic treatments are more effective in females than in males, because of the more prominent Th2 response in females • Females with moderate AD and moderate impact on quality of life are undertreated • Females report higher rates of adverse events
• During pregnancy, only cyclosporine may be used off-label in severe disease, when the benefits exceed the potential side effects. • Evidence on the safe use of dupilumab during pregnancy is accumulating
• Appropriate counselling about the disease course and treatment during pregnancy and lactation must be offered to patients planning a pregnancy

no augmented risk of AEs and suggested even a reduced risk of preterm labor [72]. However, in the current guidelines, dupilumab is still not recommended during pregnancy because of the scarce evidence on safety [44, 47, 68]. Tralokinumab and lebrikizumab use is avoided during pregnancy as a precautionary measure. No washout period before conception is specified for biologics. Current evidence on the use of JAK inhibitors (abrocitinib, baricitinib, and upadacitinib) during pregnancy is very limited. JAK inhibitors have shown potential teratogenic effects in animal models. Most reports are individual cases of retrospective reviews of clinical trials, limited in quantity of patients. Nevertheless, all cases reported favorable pregnancy outcomes, with similar rates of spontaneous abortion and congenital malformations, compared to the general population [47, 73]. JAK inhibitors remain contraindicated during pregnancy. In addition, it is currently advised to discontinue JAK inhibitors 4 weeks prior to conception [47, 65]. JAK inhibitors are transferred into breast milk; therefore, their use is contraindicated during breastfeeding [73]. Recommendations for the use of each treatment in pregnancy, based on the European guidelines (EuroGuiDerm) on atopic eczema [46] are reported in Table 1. It is important to consider that undertreatment of AD during pregnancy may lead to serious deterioration in the quality of life, and to complications such as skin infections.

3. Conclusions

Gender medicine aims to provide personalized care that accounts for both biological and social factors, ultimately improving health for all individuals. The medical and scientific communities are contemplating the differences between sexes in the management of patients, and gender medicine has been achieving increasing importance. It is relevant that dermatologists consider that sex may strongly affect biological processes underlining the disease, and thus affect epidemiology, clinical features, mechanisms, risk factors, treatment efficacy, social and behavioral factors, and mental health, as already proposed for psoriasis [74]. Overall, while the fundamental nature of AD is the same in males and females, there are several differences, which may affect functional impact, disease course, and treatment approaches (Table 2). Recognizing these variations can lead to more appropriate treatments.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Disclosure

All authors read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Martina Maurelli wrote the manuscript and Paolo Gisondi and Giampiero Girolomoni revised the manuscript.

Funding

This study was supported by the Grant number 848028—Decision on optimal combinatorial therapies in Immune-Mediated Inflammatory Diseases using systems approaches (DocTIS)—Horizon 2020.

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