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POSITION STATEMENT

European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period

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Abstract

Atopic dermatitis (AD) is a common inflammatory skin disease that affects both children and adults, including a large number of adults of reproductive age. Several guidelines for the treatment of AD exist, yet specific recommendations for the treatment of pregnant or lactating women and for adults planning to have a child are often lacking. This position paper from the European Task force on Atopic Dermatitis (ETFAD) is based on up-to-date scientific literature on treating pregnant and lactating women as wells as adults with AD planning to have a child. It is based on the expert opinions of members of the ETFAD and on existing safety data on the proposed treatments, many of which are derived from patients with other inflammatory diseases or from transplantation medicine. For treating future parents, as well as pregnant and lactating women with AD, the use of topical treatments including moisturizers, topical corticosteroids, tacrolimus, antiseptics such as chlorhexidine, octenidine, potassium permanganate and sodium hypochlorite (bleach) is deemed to be safe. Ultraviolet (UV) therapy may also be used. Systemic treatment should be prescribed only after careful

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consideration. According to the opinion of the ETFAD, treatment should be restricted to systemic corticosteroids and cyclosporine A, and, in selected cases, azathioprine.

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Conflicts of interest

Dr. Vestergaard is consultant, investigator and has received grants from Novartis, Sanofi Genzyme, Leo Pharma, Pierre Fabre, AbbVie, MEDA, Galapagos and Eli Lilly. Dr. Wollenberg has received grants, personal fees or non-financial support from Almirall, Anacor, Astellas, Beiersdorf, Bioderma, Celgene, Chugai, Galderma, Hans Karrer, LEO Pharma, L'Oreal, MEDA, MedImmune, Merck, Novartis, Pierre Fabre, Pfizer, Regeneron and Sanofi Aventis. Dr Barbarot received research grants, personal fees and non-financial support from Pierre Fabre Laboratory and Fondation pour la dermatite atopique; from Bioderma, Laboratoire La Roche-Posay, Sanofi Genzyme, AbbVie; and from AbbVie, Novartis, Janssen. Dr. Christen-Zaech has been an advisor, speaker, investigator for or has received grants form Galderma, La Roche-Posey, Pierre Fabre, Permamed, Pfizer, Procter and Gamble, Eli Lilly, AbbVie and Sanofi Genzyme. Dr Deleuran is a consultant, investigator, member of scientific advisory boards and/or lecturer for AbbVie, Eli Lilly, Galapagos, Leo Pharma, MSD, Novartis, Pfizer, La Roche-Posay, Roche, Regeneron, Sanofi Genzyme and Pierre Fabre. Prof. dr. Phyllis Spuls has done consultancies in the past (>2 years ago) for Leo Pharma, Anacor, AbbVie, Janssen Pharmaceutica and Novartis, more recently for Sanofi 111017 and AbbVie 041217 (unpaid), received independent research grants in the past from Schering Plough (>5 years ago) and Leo Pharma (>3 years ago) and is involved in contract research to participate in clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of, for example, psoriasis and atopic dermatitis: financial compensation is paid to the hospital. Dr. Carsten Flohr has not handed in his COI information yet. Dr Carsten Flohr holds a UK National Institute for Health Research (NIHR) Career Development Fellowship (CDF-2014-07-037). His department has received research funding from Sanofi. CF is also supported by the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. Dr. Magdalena Trzeciak has been lecturer and/or investigator for LEO Pharma, Pierre Fabre. Dr. Laura von Kobyletzki has received research grants and was paid lecturer and member of scientific advisory boards for Sanofi Genzyme. Dr. Julien Seneschal has been consultant and investigator for AbbVie, Sanofi Genzyme and Leo Pharma. Dr Carle Paul has been consultant and investigator for AbbVie, Almirall, Amgen, Boehringer, Celgene, Janssen Cilag, Leo, Lilly, Pfizer, Novartis, Pierre Fabre, Sanofi and UCB. 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Introduction

Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin disease that affects 15–20% of children and 2–5% of adults.[1] AD manifests itself clinically with erythema, papules, xerosis and scaly skin in an age-specific anatomical distribution. AD is a multifactorial disease, and its complex etiopathogenesis involves altered immune responses and a dysfunctional skin barrier. Recent studies have proposed that AD, similar to other inflammatory skin diseases, is a systemic disorder with circulating cytokines and chemokines affecting other organs as well. AD is often associated with concomitant allergies and secondary cutaneous infections. The negative impact of AD on quality of life is one of the highest among all chronic inflammatory skin diseases.[2] Moreover, AD can have a dramatic impact on sexual health,[3] including difficulties with conceiving a child. This underscores the importance of controlling the disease in both male and female patients before conception.

Since AD persists into adulthood in about 20% of cases,[4] caregivers need to be informed about safe and effective management of AD in patients of reproductive age. Treating pregnant or lactating women and future parents (see Table 1 for definitions) with AD can be a challenge since no large clinical studies on its possible effects and side-effects on conception, pregnancy, the unborn child and lactation are currently available. As some recommendations tend to suggest limiting or avoiding active therapy preconceptionally, prenatally and during lactation, physicians are sometimes too restrictive in prescribing both topical and systemic treatments during these periods. This observation was recently supported in a registry study from Denmark, where less potent topical steroids were used during pregnancy compared with before pregnancy.[3] This may result in inadequate control of AD, potentially leading to flares and infections, and may have a detrimental effect on the health of women during pregnancy as well as a serious impact on sexual health.[5]

Recently, in a critical appraisal of the topic, the evidence of pregnancy and fetal outcomes after paternal exposure to azathioprine, methotrexate or mycophenolic acid was summarized; however, the literature was very sparse and mainly of an observational character.[6] In the 2015 European Task Force on Atopic Dermatitis (ETFAD) position paper on treatment of AD, we listed systemic agents that were absolutely contraindicated during pregnancy, including methotrexate, alitretionine and mycophenolate mofetil, whereas cyclosporine A and azathioprine were recommended as drugs that could be used in certain instances.[1] The ETFAD recognizes that a much more detailed position paper is needed on the treatment of pregnant and lactating female AD patients, as well as male and female AD patients who are planning a pregnancy. This expert position paper of the ETFAD expresses the opinions and experiences of the ETFAD members, and provides, where possible, the scientific background for these opinions and experiences. It is therefore not intended as a guideline. For current guideline information, please refer to the current literature.[7–13] It is also important to stress that pregnancy in itself is not a disease, even if treatment of pregnant women requires thorough considerations of the benefits and risks of the treatment modalities available. This position paper and the recommendations provided cannot supersede local/national guidelines, common sense, good clinical work and the individual response of doctors treating patients (Fig. 1).

The paper is divided into two parts: the first part focuses on women of reproductive age, before and during pregnancy as well as during lactation; the second part concentrates on men wishing to father children.

Background risk for pregnancy complications

The worldwide number of stillbirths is estimated to be 3.2 million year, 3% of all births. It differs from 5 to 32 per 1000 pregnancies depending on the country.[14] Causes are unexplained in 25–60% of cases. Known risk factors are smoking during pregnancy, exposure to environmental smoke, advanced maternal age and high/low body mass index.[15,16]

Table 1 Definitions

Women	Preconceptive	Women of reproductive age, in the period of time were they actively have decided to try to conceive
	Pregnant	Women who are pregnant and determined to carry the child full term until birth
	Lactating	From the time of birth until the child is weaned off and breastfed, irrespective of additional foods
Men	Preconceptive	Men who are trying to father a child

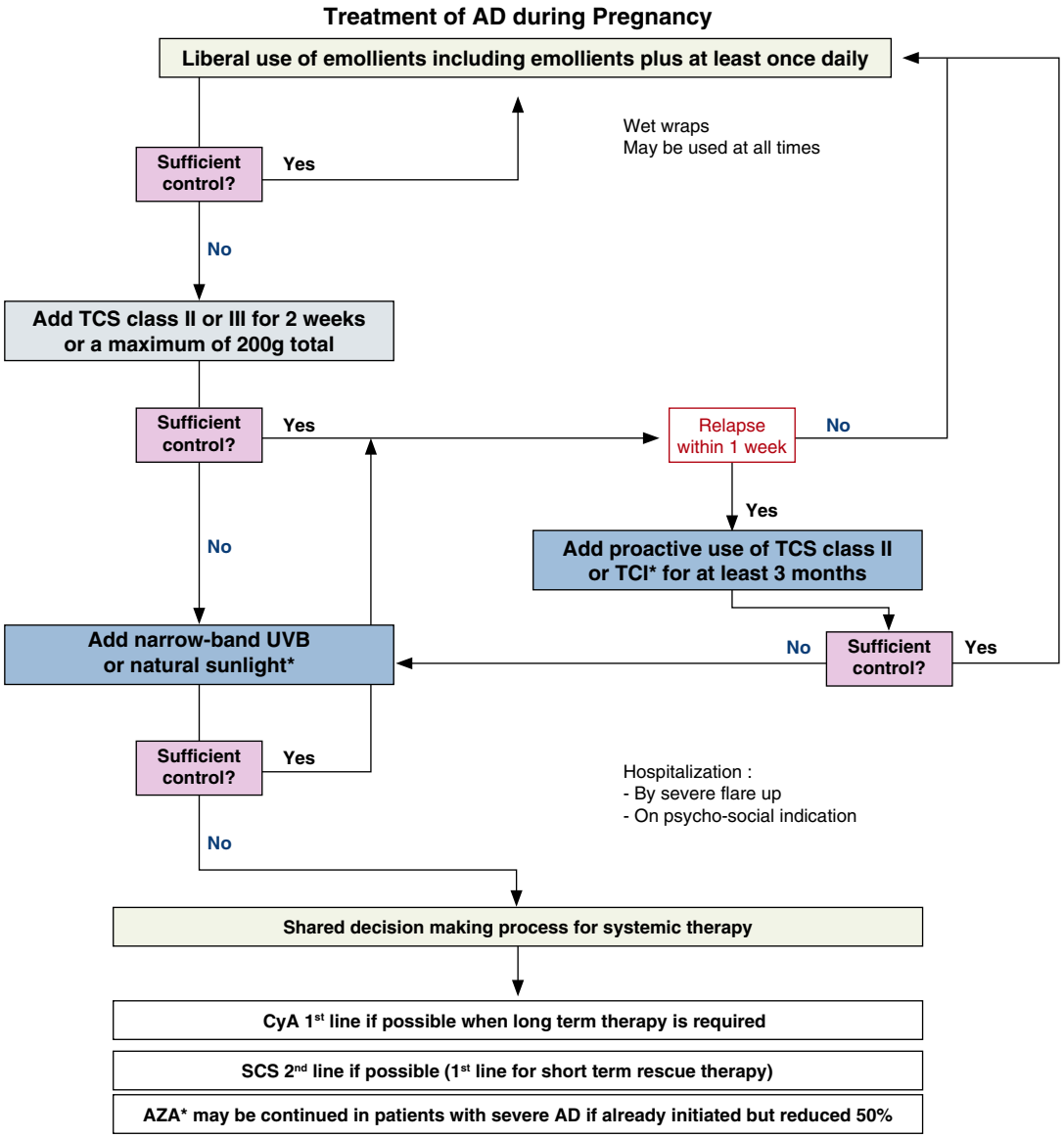

Figure 1 Algorithm for the treatment of pregnant women with atopic dermatitis. The algorithm illustrates the recommendations of the ETFAD in brief, please consult the text for details.

Every year, about 8 million children, 6% of all births worldwide, are born with severe congenital malformations, with variation depending on which country is studied.[17] The most common serious birth defects include congenital heart defects (CHD), neural tube defects and Down syndrome.[17] Severe CHD such as single ventricle, atrioventricular septal defects and tetralogy of Fallot are increasing in incidence in Europe.[18] Risk factors for these malformations are maternal obesity and diabetes. The increased incidence of cystic adenomatous malformation of the lung and the decreased prevalence of limb reduction defects are unexplained. Oesophageal atresia, duodenal atresia/stenosis and anorectal atresia/stenosis have seen an approximate annual increase in the prevalence of 3% over the last decade.[18]

According to the World Health Organization (WHO), approximately 5% (ranging from 1% to 10%) of congenital anomalies are associated with environmental exposures such as air pollution, cigarette smoke, pesticides, solvents, metals, radiation, contaminants and chemicals.[17]

Thus, even though a drug may be considered safe to use during pregnancy, malformations and stillbirths are bound to happen, also in patients with AD and patients who are treated with a drug.

Clinical presentation of AD in pregnant women

AD is the most common general skin disease in pregnancy.[19] It may be a pre-existing condition in pregnant women, or it may be reactivated in patients with a past AD history. Worsening of AD is mostly reported during the second and third trimesters. Clinically and histologically, there is no difference between AD observed among pregnant and non-pregnant patients. "Atopic eruption of pregnancy" (AEP) is the most common specific pregnancy dermatosis, accounting for 50% of patients seen for skin rash during pregnancy.[3] AEP may occur as a result of natural maternal T helper (Th) cell deviation during pregnancy. Most patients with AEP (80%) have no AD history or have had it in childhood only, supporting the idea that AEP may be an independent eczematous disease distinct from AD, although there are currently very limited insights into its pathogenesis. In these patients, AEP typically occurs during the first trimester of pregnancy. A minority of AEP patients (20%) have pre-existing chronic AD and experience a worsening of their AD. Clinically, most patients present a diffuse dermatitis very similar to AD, although it often lacks lichenification and flexural dominance. Some patients have a predominant prurigo type (20%). The main symptom of AEP is the relentless itch.[8,9] Indeed, only a minority (5%) experience improvement in the signs and symptoms of their skin disease during pregnancy.[4–6]

AEP presents with highly variable clinical manifestations. The differential diagnosis is quite broad and may include contact dermatitis, pruritic urticarial papules and plaques of pregnancy, drug eruptions, polymorphic eruption of pregnancy, pemphigoid gestationis and mycosis fungoides. Systemic therapeutic strategies discussed in this paper refer mostly to patients with pre-existing chronic AD, yet the treatments may also be used for AEP.

Factors that may explain change in atopic dermatitis severity during pregnancy

Several factors may contribute to a worsening of AD during pregnancy. During this time, the immune system is normally skewed towards a Th2-dominated response, as this reduces the immunological response against the fetus, who is antigenically different from the mother,[20] and hence reduces the risk of miscarriage. Skewness towards a Th2-dominated response enhances a humoral response, crucial to IgE induction. AD is considered predominantly a Th2-initiated (and mostly Th2-dominated) disease with high production of interleukins (IL)-4, IL-5, IL-13, IL-22 and IL-31. The hypothesis suggests that the immunological state of pregnant women represents an agonist for AD worsening. However, the Th2 perception of the immune response in AD is complex, and cellular infiltrates also include Th1, Th17 and Th22 cells, as well as many other cytokines such as IL-25, IL-31 and IL-33.[21–23] It is currently unknown whether the expression of these cytokines changes during pregnancy and whether this can result in AD worsening or improving.

The physical and psychological stress of pregnancy may also aggravate pre-existing AD, potentially driving a vicious circle of ever-deteriorating AD.[24,25] It is well-established that there is an important psychological component in AD where stress and sleep deprivation, in particular, can worsen the disease. However, there is no evidence that AD in itself may cause fetal damage; rather, it is the complications of AD that pose a risk.

Little is known about treatment patterns during pregnancy, but patients and caregivers tend to reduce the use of topical and systemic therapies during pregnancy to avoid presumed harm to the fetus. Indeed, a recent Danish register-based study showed that ultraviolet therapy was particularly prevalent in the AD group during pregnancy, because it is considered a non-invasive treatment.[3] Moreover, pregnant AD women had overall reduced consumption of both topical and systemic medications when compared to the period prior to their pregnancy. The data did not show whether this decrease was due to resolution of dermatitis or resulted from a tapering off of treatment due to concerns about adverse drug reactions during pregnancy. However, increased use of prednisolone in this cohort during pregnancy could indicate that some patients may have been undertreated and therefore needed rescue therapy with a systemic drug.[3]

Treating a pregnant woman with AD with either topical or systemic drugs may affect the unborn child. This naturally leads to a certain unwillingness to pursue, in particular, systemic therapies and may deter patients and physicians from using effective drugs in pregnant women. However, it must be considered that untreated AD potentially puts the mother and her unborn child at risk of serious complications, such as eczema herpeticum or staphylococcus aureus infections.[26] A recent study also showed that maternal AD increased the risk of neonatal septicaemia, although this complication was very rare.[3] Moreover, exacerbation of AD may lead to impaired quality of life, anxiety and mood changes. Interestingly, some studies have indicated that maternal stress during pregnancy may play a significant role in the development of AD in offspring. It is possible that in cases where pregnant women suffer not only from AD but also from depression or psychosomatic disorders, the offspring have a significantly higher risk of developing AD up to the age of 18–20 years.[27–34] Possible psycho-immunological pathways are changes in cytokine levels[21] or oxidative stress transferred by the placenta.[35] Psychosocial job strain in general and alcohol intake during pregnancy in particular[36,37] are significant risk factors for AD development in offspring, with alcohol intake being the most prominent risk factor.[38,39]

Topical treatments of atopic dermatitis during pregnancy and postnatal period

Moisturizers

According to the 2015 ETFAD position paper on AD and other guidelines and textbooks, basic emollient therapy is key in the treatment of AD.[1,7,9,12,40] There is no firm evidence on which emollient should be used, but using one with high a lipid content and as few potentially harmful agents as possible is recommended. As a general rule, all cosmetics and cosmeceuticals including the novel category of "emollients plus" have been labelled as safe.[12,41]

It is the recommendation of the *ETFAD* that emollients, preferentially in a '*soak-and-seal*' technique, must be used as basic therapy. The emollient must be chosen on a patient-individual basis. There is no evidence against the use of paraffin-based products. Using emollients in a wet wrap technique is encouraged.[42]

Topical corticosteroids

Women	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis
	Pregnant	TCS class II or III are recommended. If the use exceeds 200 g/month, additional UV treatment should be considered. Class IV may be used as rescue therapy, or over longer periods on limited skin areas. Fluticasone propionate should be avoided.
	Lactating	Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding.
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

Topical corticosteroid (TCS) application represents the first-line treatment of AD, also during pregnancy. It has the advantage of delivering the active drug directly at the target organ, thus minimizing systemic side-effects. The same local side-effects may occur with inappropriate and excessive use in pregnant and non-pregnant AD patients. They include atrophy, striae, hypertrichosis and bruising easily. If strong TCS is used extensively, systemic absorption may occur, which can lead to Cushing syndrome, insulin resistance/diabetes and hypertension.

TCS may be used as proactive therapy or as reactive therapy in the non-pregnant and pregnant patients, depending on the severity and degree of recurrence of the symptoms.[40] Twice-weekly TCS application as maintenance therapy is regarded as safe, but caution is recommended when using potent TCS over large body surface areas (see recommendation below).[1]

There is no association between TCS use during pregnancy and increased risk of orofacial cleft in offspring. This has been reported once,[43] but this claim has since been rebuked, because no supporting data could be found.[44,45] Furthermore, two Danish registry studies found no increased risk of other malformations or preterm delivery in children whose mothers were treated with TCS during pregnancy.[46,47]

Overall, these findings are in concordance with a Cochrane review, updated in 2013, which included 14 observational studies (a total of 1 601 515 pregnancies) in which no association was found between TCS use during pregnancy and preterm delivery, birth defects (hypospadias, orofacial cleft), fetal death or low Apgar scores. There was, however, a non-significant association between using potent to very potent TCS and increased risk of low birthweight. Overall, the level of evidence was classified by the authors as 'very low' since all studies were observational, and variation observed in the results of the included studies was high.[48] In conclusion, several studies have examined the risk of TCS use in pregnancy, and overall, it has been deemed safe, although the use of very potent topical corticosteroids may be associated with low birthweight. There is an exception, though fluticasone propionate is the only TCS that is known not to be metabolized by the placenta and therefore should not be used in pregnant women.[49]

No studies have examined the safety of TCS use during lactation. Nevertheless, applying the topical treatment in the nipple region immediately after nursing the child, to allow the drug to be absorbed into the skin before the next feeding, is recommended. Additionally, care should be taken to gently clean the nipple for remaining TCS before nursing.

In the authors' experience, class I TCS, according to the Niedner classification,[50] is not potent enough for AD treatment, class II TCS is suitable in most situations, class III TCS may be used in the short term with the same precautions as in non-pregnant patients, and class IV TCS is to be avoided. According to their labels/summary of product characteristics (SmPCs), most TCS is not contraindicated during pregnancy, but restrictions like "careful indication" are common. In addition, the modern TCS of the 4th generation according to Copeman, which are double estered in C17 and C21, should preferentially be used. These include prednicarbate, hydrocortisone aceponate, hydrocortisone butyrate, methylprednisolone aceponate and hydrocortisone buteprate.[51]

It is the recommendation of the *ETFAD* that the lowest possible potency of TCS, preferably of the 4th generation, should be used and that class II (e.g. prednicarbate) or class III is used, although with special care, in skin areas prone to striae formation, e.g. breasts, thighs and abdomen. However, if the amount of TCS used exceeds 200 g/month, other treatments including ultraviolet (UV) therapy should be considered. Class IV TCS should be avoided during pregnancy, although they may be used in very localized chronic/lichenified lesions and as rescue therapy.

Topical Calcineurin inhibitors

Women	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis
	Pregnant	No restrictions compared to the ETFAD position paper on atopic dermatitis
	Lactating	Should be applied immediately after breastfeeding, and nipples should be cleaned gently and carefully before feeding
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

The recommendation is for tacrolimus since there is not ample data for pimecrolimus available.

There are no studies on the use of topical calcineurin inhibitors (TCI) during pregnancy. However, oral tacrolimus has been used in pregnant women following solid organ transplantation, and CyA has been used even more widely in pregnant patients with organ transplants. Observational studies have found no increased risk of congenital malformations, but did find an increased risk of prematurity, possibly associated with the maternal disease. Birthweight was consequently found to be significantly decreased, but fitting, for gestational age.[52,53]

No studies on the use or effect of topical tacrolimus during pregnancy have been published. Systemic absorption of topical tacrolimus is, however, very low in both 0.1% and 0.03% concentrations due to the large size of the molecule,[54–56] although a very impaired skin barrier as seen in Netherton syndrome may allow absorption.[57] Taken together with the large experience on systemic use of calcineurin inhibitors in organ transplant patients, available data suggest that the risk of congenital defects is not increased. Consequently, TCI may be preferable for use on the face and intertriginous areas and on abdominal, breast and thigh skin, where the risk is of striae formation increases with excessive use of TCS.

No studies have been published on the use or effect of topical pimecrolimus during pregnancy. Studies of topical pimecrolimus show that it is absorbed to an even lower degree than tacrolimus.[58] According to their labels and SmPCs, both TCIs should not be used during pregnancy because of lack of experience, but no recommendations exist concerning preconception use.

It is the recommendation of the *ETFAD* that the off-label use of TCI during pregnancy is justified based on significant experience from systemic use of oral calcineurin inhibitors in transplant patients, and on the clinically apparent, favourable benefit/risk ratio of TCI, along with the minimal absorption and apparent safety of systemically administered calcineurin inhibitors. Moreover, tacrolimus ointment is the recommended TCI during pregnancy due to the larger amount of existing data. A similar recommendation is made for breastfeeding women with AD. As with TCS, there are no studies on the use during lactation. The ETFAD recommends the same approach as with TCS, apply after nursing the child and gently clean the nipple for any remaining TCI before nursing the child.

Topical PDE-4 inhibitors

Women	Preconceptive	Not recommended
	Pregnant	Not recommended
	Lactating	Not recommended
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

Crisaborole (Eucrisa) is a new boron-based topical benzoxaborole PDE4 inhibitor with a molecular weight of 251 D, which acts by diminishing the levels of cyclic adenosine monophosphate.[59] Studies of safety have shown minimal systemic absorption[60]; yet, there is no information on preconceptional use and use during pregnancy or lactation. According to the label, crisaborole is contraindicated in pregnant women.

It is the recommendation of the ETFAD that, due to lack of experience with this drug during pregnancy, crisaborole should not be used preconceptionally in pregnancy or during lactation.

Topical antiseptic compounds

In all AD patients, *Staphylococcus aureus* may worsen AD through the release of superantigens.[61] In general, eczematous skin was shown to have an increased risk of overgrowth of *Staphylococcus aureus*.[62] The ETFAD position paper from 2015 recommends the use of antiseptics in the treatment of AD during acute flares and when there is evidence of staphylococcal infections.[1] The choice of topical antiseptics may vary from country to country, while some of the most widely used agents are chlorhexidine, triclosan, octenidine, diluted sodium hypochlorite (bleach) and potassium permanganate.

Chlorhexidine is contained in various liquid soap and syndet products, as well as in oral rinse formulations (mouth wash). No controlled studies have addressed potential teratogenic effects in pregnant women. The preparations are generally available without prescription, and there are no warnings against their use preconceptionally or during pregnancy and lactation. In an oral mouthwash, chlorhexidine is described as unproblematic even for long-term use.[63] A study of chlorhexidine diacetate on rat embryonic limb bud cells showed cytotoxicity but no evidence of teratogenicity.[64]

Triclosan is a polychloride-phenoxyphenol with strong antiseptic efficacy and is known as an endocrine hormone disruptor in rats.[65,66]

Octenidine is a gemini-surfactant structure which is active against Gram-positive and Gram-negative bacteria. There are no data on the use of this compound preconceptionally or in pregnant or lactating women with AD. However, it has been used for

the treatment of vaginal dysbiosis during pregnancy and through that prevented preterm birth, without any increase in the risk of congenital malformations.[67]

Sodium hypochlorite and potassium permanganate have been used for decades as disinfectants. Sodium hypochlorite has also been used in public swimming pools, and there is ample experience that they do not cause harm to the fetus, although no prospective studies are available. Watery solutions of any of these are not harmful to adults or small children and can be used in pregnant women.

It is the recommendation of the ETFAD that antiseptics, except triclosan, may be used by pregnant women if clinically needed to prevent recurring infections, but not as a general measure in all patients.

Topical antibiotic drugs

In general, topical antibiotics should be used restrictively as they increase the risk of bacterial antibiotic resistance. The minimal inhibitory concentration (MIC) value is very difficult to control, and sub-MIC concentrations are very likely to occur. If localized skin infections with *Staphylococcus aureus* that cannot be handled with antiseptics occur, topical antibiotics may be used. An escalation of the potency of TCS to treat eczema is generally preferred over the use of topical antibiotics and is the recommended strategy.

Fusidic acid and mupirocin are very commonly used topical antibiotics,[68] and no literature on any harmful effects due to their use during pregnancy has been published. The systemic absorption of these drugs is very low. The labels state they may be used during pregnancy, although with caution. Fusidic acid is preferred over mupirocin for AD treatment, because in most countries mupirocin is reserved for eradication of MRSA in the nasal cavity.

Aminoglycosides are a useful substance class for Gram-negative bacterial infection and are also available in topical formulations, but are largely unsuitable for AD because the efficacy spectrum does not meet the clinical needs of AD patients, and because resistance and contact sensitization can occur with prolonged use. They are not recommended for treatment of AD patients. According to their labels, topical fusidic acid and mupirocin should be used with care in pregnant women, whereas aminoglycosides are not recommended for treatment of AD irrespective of pregnancy.[1]

It is the recommendation of the ETFAD that topical fusidic acid can be used for treatment of small areas of clinically infected AD in pregnant women and that aminoglycosides should be avoided for treatment of AD in general. Mupirocin may be used for eradication of MRSA in the nasal cavity if needed.

UV therapy

Pregnant women have been exposed to natural sunlight for thousands of years without any apparent negative side-effects. However, no studies on the use of UVA or UVB therapy in pregnant women have been published. Studies of women exposed to high levels of UVB as a result of outdoor jobs during pregnancy have shown no increased risk of malformations.[69] Studies have shown that therapy with UVB decreases folic acid levels, and this should be taken into consideration with folic acid supplements preconceptionally and during the first trimester.[70] Phototherapy, however, may exacerbate pregnancy-induced hyperpigmentation such as melasma, and care should therefore be taken.

There is a theoretical risk of psoralens being mutagenic; however, a Swedish study from 1993 investigating 504 infants born after oral PUVA therapy compared with 689 controls showed no increased risk of malformation. An increased risk of low birthweight was observed, but the authors attributed this to an increased number of smoking mothers in the treatment group.[71]

In summary, broad-spectrum and narrow-band UVB (including narrow band; 311 nm) therapy does not impose a risk to the fetus in pregnant woman.

According to the label (FDA), psoralen should not be used preconceptionally (3 months) or in pregnant and lactating women.

It is the recommendation of the ETFAD that narrow-band UVB as well as UVA1 can be used liberally in patients where this treatment is feasible, but the ETFAD advises against the use of psoralens.

Treatment of AD-related complications

A limited number of infectious complications, mostly due to *Staphylococcus aureus*, herpes simplex virus and malassezia furfur, are associated with AD and may also occur during pregnancy. A limited number of anti-infective agents are clinically well-established for their treatment during pregnancy.

A clinically characteristic oozing resulting in yellow crusts from dried serum is the diagnostic hallmark of impetiginization, which is an infection with *Staphylococcus aureus*. Small areas may be treated with a combination of topical antiseptics or fusidic acid, whereas large areas exceeding 2% of the body surface area should be treated with systemic antibiotics according to local guidelines and antibiotic resistance patterns. First-generation oral cephalosporins are a safe and in most cases adequate treatment option during pregnancy.[1,12]

A disseminated, distinctly monomorphic eruption of dome-shaped vesicles, accompanied by fever, malaise and lymphadenopathy is suggestive of eczema herpeticum (EH).[72,73] EH is a potentially serious or even fatal complication of AE, especially for children and pregnant women who will need immediate medical action.[73] Though acyclovir is not licensed for use in pregnant women, there is ample clinical experience of acyclovir use during pregnancy. A Danish registry study involving 1800 females and the manufacturer's database all indicate that its use in pregnancy is safe.[26] Therefore, the mainstay of EH therapy is prompt systemic antiviral chemotherapy with intravenous (i.v.)

acyclovir in standard dose, and it is the opinion of the authors that it should be initiated without delay once clinical suspicion of EH is raised,[74] preconceptionally and in pregnant and lactating women.

A 'head-and-neck-pattern', sometimes associated with a slightly brownish discoloration, is a clinical hallmark of a malassezia furfur infection that can occur in AD patients. IgE antibodies and atopy patch test reactions have been demonstrated against this agent.[75,76] The use of topical ketoconazole, predominately as a shampoo 2%, may be used to reduce colonization as well as eczema severity. According to the label, continuous use of ketoconazole 2% shampoo does not result in detectable plasma levels following chronic use on the scalp and therefore does not seem to pose any risk to the fetus. According to the label, it may be used during pregnancy and lactation when potential risks outweigh benefits. In conclusion, no apparent risk is associated with using ketoconazole- or ciclopirox olamine-containing over-the-counter (OTC) shampoos in pregnant women.

It is the recommendation of the ETFAD that acyclovir may be used systemically and that ketoconazole and ciclopirox olamine may be used topically for treatment of infectious AD complications in pregnant women. Antibiotics may be needed and should be used according to local guidelines. The ETFAD recommends using oral cephalosporins or flucloxacillin if no specific local guideline exists.

Systemic anti-inflammatory treatment of atopic dermatitis in pregnant patients

The challenges regarding the use of systemic immunosuppressant drugs in pregnant and lactating women are well-known. A large proportion of patients with AD are women and men of reproductive age, and some of the systemic drugs prescribed in the treatment of AD are potentially teratogenic; for others, there is insufficient experience of use in human pregnancies. Therefore, couples wishing to conceive, as well as pregnant and lactating women with AD, need adequate and safe treatments and support, which is best given on a patient-individual basis and often in close collaboration with an obstetrician. Evidence is based on observational studies and is often limited.

Vaccination of the child after birth by a mother receiving immunosuppressive therapy may also be an issue that should be considered. Even though treatment may be deemed to be safe in terms of malformations and pregnancy outcome, the child may still be immunocompromised from the drug crossing the placenta, as discussed in the context of TNF-alpha blockers. In a review paper of vaccinations of children treated with immunosuppressive drugs for inflammatory bowel disease, it is recommended that treatment be paused for 3 months before vaccination since this would be safe both in case of toxoids but also live vaccines.[77] Most European vaccination programmes of infants are not commenced until the age of 2 months and should thus be deemed safe.

Corticosteroids

Systemic corticosteroids (SCS) are a well-researched, fast-acting, body-own substance class influencing a broad spectrum of regulatory pathways in the human body, some of which are anti-inflammatory. They are occasionally used in non-pregnant AD patients for short-course treatment in acute and severe flares.[78] The risk/benefit ratio is largely unfavourable.[1] SCS are not recommended for long-term use due to their serious side-effects, which include osteopenia, osteoporosis, type 2 diabetes, hypertension, glaucoma, infections, adrenal suppression, striae formation, acne and others.[1] During pregnancy, SCS may also increase the risk of gestational diabetes, preeclampsia and even membrane rupture and preterm delivery.[79] Repeated treatment courses may lead to decreased birthweight and a higher incidence of gastrointestinal reflux.[80–82] Studies of the use of SCS during pregnancy have shown no risk of teratogenicity, but repeated treatment courses may lead to decreased birthweight and higher incidence of gastrointestinal reflux.[80–82] Earlier studies have suggested an increased risk of oral clefts when the mother was treated with SCS during pregnancy, but this association could not be confirmed in a Danish study of 1449 women who used inhaled or oral corticoids preconceptionally or during the 1st trimester.[83]

SCS seem to be safe to use in pregnant women provided proper monitoring of the mother, and child is undertaken. However, current guidelines discourage the use of SCS, even in non-pregnant women,[13] and other therapies should be prioritized over SCS, e.g. escalation of TCS.

Treatment with SCS during lactation is safe, since <0.1% of the mother's ingested dosage is secreted into breastmilk.[84,85]

The literature on suppression of the hypothalamus–pituitary–adrenal (HPA) axis in newborns is very scant. In a recent case series study of all newborns in a paediatric centre in the Netherlands that was conducted over a 9-year period, only 16 children were born to mothers treated with SCS. Of these, five had hypoglycaemia with normal serum cortisol levels and two had abnormal urinary steroid profiles due to prematurity. The authors concluded that there was no evidence of prolonged neonatal adrenal suppression. However, their guideline instructs that children born to mothers treated with > 35 mg/day prednisolone should be admitted for a 48-h observation period.[86]

In the authors' experience, SCS are rarely needed in pregnant AD patients. If needed, short-term use of the substance class is possible, but only up to 0.5 mg/kg/day. As there is high variation of inactivation of SCS in the placenta depending on the molecular structure of the drug, SCS with a high grade of inactivation should be chosen to restrict treatment largely to the mother while minimizing as much as possible co-treatment of the child.[87]

It is the recommendation of the *ETFAD* that SCS use for AD be limited in general. Prednisolone, and not dexamethasone, should be used if SCS treatment is needed in pregnant AD patients. Thus, the *ETFAD* recommends using SCS only if adequately administered TCS and UV therapy has failed, and only for shorter periods of time (this is dependent on national guidelines but in general <2–3 weeks) and only up to 0.5 mg/kg/day.

Cyclosporine A

Women	Preconceptive	May be used
	Pregnant	May be used under strict indications, is first-line therapy for long-term control
	Lactating	May be used under strict indications
Men	Preconceptive	No restrictions

Cyclosporine A (CyA) inhibits the actions of calcineurin, which, in turn, causes inhibition of translocation of the nuclear transcription factor of activated T cells (NFAT). NFAT, in turn, leads to diminished transcription of many pro-inflammatory cytokines including IL-2. CyA is a fast-acting drug with a high degree of efficacy, but with potentially harmful side-effects such as decreased renal function.[88] Most knowledge of the effects and potential side-effects of this drug on the fetus during pregnancy comes from studies of solid organ transplant patients. CyA crosses the placenta, and the serum concentration of the fetus is up to 64% of that of the mother.[89–91] However, all studies and meta-analyses showed no increased risk of congenital malformations or fetal death compared to the background populations.[92,93] Yet, an increased risk of low birthweight may exist.[94] Overall, CyA seems to be a safe treatment alternative in AD cases that are recalcitrant to other therapies. However, extra attention should be given to the renal function and blood pressure of the mother during pregnancy.

CyA is secreted in breastmilk and may be transferred to the fetus.[95] However, case series and case reports describe children of women with solid organ transplants who against physician recommendation have breastfed their children without adverse effects in their children.[96,97] It has been suggested that mothers treated with cyclosporine A could breastfeed their children as long as the child's CyA serum concentrations are monitored.[98] However, this recommendation was given for solid organ transplant patients for whom immune suppression is vital for survival of the graft, whereas for AD, using cyclosporine A in lactating mothers is generally not recommended. The authors have some experience with CyA treatment during pregnancy, which supports the positive safety assessment of the literature review. According to the FDA label, CyA may be used during pregnancies under special circumstances, and the FDA label states: '*Cyclosporine A should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the foetus*'.

It is the recommendation of the *ETFAD* that CyA be used off-label in pregnant and lactating women with AD if topical treatment and UV irradiation treatment options fail and there is a clear need for better long-term disease control. It is currently regarded the default method of immunosuppressive treatment during pregnancy in cases where continuous treatment is needed where as SCS may be used in acute flare-ups and need for immediate and short-term control, if all restrictions for non-pregnant females are considered.

Azathioprine

Women	Preconceptive	May be used
	Pregnant	May be used under strict indications if no other therapy is possible. It is not recommended to initiate therapy during pregnancy where other therapies should be used.
	Lactating	May be used, but it is recommended to discard milk produced within 4 hours after drug intake.
Men	Preconceptive	No restrictions.

Azathioprine (AZA) is a prodrug converted into many breakdown products, of which 6-mercaptopurine (6-MP) is the most important. The drug interferes with the synthesis of purine, a nucleoside, and thereby inhibits DNA synthesis. The drug and its active metabolites are degraded by the enzyme thiopurine-S-methyltransferase, and individuals with a TPMT gene mutation may achieve higher serum concentrations of 6-MP than persons without this mutation.[99] Azathioprine acts mainly on fast-dividing cells, e.g. the T lymphocytes in AD.[100] No consistent reports of congenital defects caused by treatment with azathioprine in patients with inflammatory bowel disease have been issued.[101,102] The risk of preterm delivery has been described with conflicting evidence, as confounding by indication has been a concern.[103]

AZA may therefore be used off-label in pregnant women with severe, uncontrolled AD in whom topical, UVB and other systemic therapy fails. Closely consulting an experienced obstetrician when prescribing this drug is strongly recommended.[104]

The use of AZA during lactation is debated. The WHO has recommended that the potential side-effects of AZA outweigh the effects and benefits of the treatment,[105] and studies suggest that AZA intake during breastfeeding could increase the long-term risk of immunosuppression and carcinogenesis in the child.[106] Yet, other studies do not confirm this finding and conclude that AZA may be used during lactation.[85,107,108] A blood count to monitor for signs of immunosuppression in the child at the age of 4 weeks can be considered.[109]

The authors have little experience with AZA treatment during pregnancy, but its use is more common in pregnant women with inflammatory bowel disease.

According to the FDA label, azathioprine is contraindicated during pregnancy, and the label states that 'Azathioprin (*IMURAN) should not be given during pregnancy without careful*

weighing of risk versus benefit. Whenever possible, the use of Azathioprine (IMURAN) in pregnant patients should be avoided'.

It is the recommendation of *the ETFAD* that AZA use during pregnancy should be avoided as there are better alternatives. As AZA has been used for treating pregnant women with other systemic inflammatory diseases without significant evidence of an increased risk of birth defects, it is not contraindicated at the same level as MTX and mycophenolate mofetil and may be used off-label in the absence of other alternatives as continuation of treatment in women already receiving this treatment at the time of conception. It is the opinion of the experts in the ETFAD that the dosage of azathioprine should be reduced to 50% if it is continued during pregnancy. The *ETFAD* does not recommend initiation of azathioprine after conception.

Methotrexate

Women	Preconceptive	Therapy must be stopped 6 months prior to desired time of conception if no local/national guideline exists. Local/National guidelines supersedes this recommendation
	Pregnant	Contraindicated
	Lactating	Contraindicated
Men	Preconceptive	Therapy must be stopped 3 months prior to desired time of conception

Methotrexate (MTX) is an antimetabolite. MTX inhibits dihydrofolate reductase, an enzyme involved in the synthesis of tetrahydrofolate, which, in turn, is needed for the synthesis of thymidine. Thymidine is one of the nucleic acids in DNA. Since MTX blocks the synthesis of new DNA,[110] the drug is associated with severe birth defects, including craniofacial abnormalities, limb defects, cardio and genital defects and mental retardation when taken during pregnancy.[111,112] Even low-dose exposure (<20 mg per week) may cause congenital defects.[113] However, the risk when using low-dose treatment seems to be lower than MTX in cancer treatment. Therefore, in cases of inadvertent exposure during early pregnancy, termination of pregnancy is not justified, but treatment should be stopped immediately and a level II ultrasound should be offered in order to examine fetal development.[114] With regard to lactation, MTX is excreted in breastmilk, but in concentrations below 10% of maternal serum concentrations. As even these low doses have been found to cause immune suppression and neutropenia in infants, MTX intake during lactation is strongly discouraged.[111] The European League Against Rheumatism (EULAR) task force recommends that MTX be stopped 1–3 months before planned pregnancies.[115]

According to the EMA label which states '*If women of a sexually mature age are treated, effective contraception must be performed during treatment and for at least six months after stopping treatment*', MTX is absolutely contraindicated during pregnancy and lactation, and also in a period of up to 6 months before conception. However, local labels in different countries suggest a contraindication range spanning from 1 month prior to conception to 6 months before conception.

The *ETFAD* acknowledges the discrepancy between the EULAR/EADV/EDF recommendations (1- to 3-month waiting period) and the EMA label (6-month waiting period). The benefit–risk of MTX for patients has to be discussed individually.

Mycophenolate mofetil

Women	Preconception	Therapy must be stopped 3 months prior to desired time of conception
	Pregnancy	Contraindicated
	Lactating	Contraindicated
Men	Preconception	Therapy must be stopped 3 months prior to desired time of conception

Mycophenolate mofetil (MMF) inhibits DNA synthesis through inhibition of purine synthesis by blockading inositol monophosphate dehydrogenase.[116] MMF is teratogenic and associated with a specific set of embryonal malformations known as MMF embryopathy, which includes microtia, aural atresia, cleft lip and palate, hypertelorism and polydactyly, as well as abnormalities in the central nervous system (CNS) and the renal and cardiovascular systems.[117,118] MMF is absolutely contraindicated in pregnant AD patients and also for male AD patients 3 months before conception. There are no data on MMF in lactating women; however, it is secreted in the milk, so breastfeeding during MMF treatment is not recommended. According to the FDA label, MMF is strictly contraindicated during pregnancy; the label states that '*women of childbearing potential must receive contraceptive counselling and use effective contraceptive while and for 3 months after stopping therapy*'.

The *ETFAD* recommends adhering to the strict contraindication of the label and never using MMF in women planning a pregnancy or in pregnant or lactating women.

Dupilumab

Dupilumab (Dupixent) is an IgG4 antibody directed against the common IL-4Rα subunit of both the IL-4 receptor and the IL-13 receptor.[119] Thus, dupilumab blocks the action of two essential cytokines in the pathogenesis of AD. When using antibodies for the treatment of AD, including dupilumab, possible passage and even active transport and up-concentration across the placenta should be considered. IgG1 is the most transported antibody, and IgG4 is the second most transported antibody.[120] In the case of dupilumab, an up-concentration in the fetus may be expected.

In the opinion of the authors, neither experimental data nor theoretical considerations point to dupilumab's teratogenic capacity. However, ample experience with CyA, AZA and SCS suggests these drugs should be used instead of dupilumab in pregnant women with AD until more experience is available.

According to the FDA label, there are no data supporting the use of Dupixent during pregnancy; the label states: '*there are no available data on DUPIXENT use in pregnant women to inform any drug associated risk*'. According to the European SmPC, Dupixent may be used in special circumstances; it states that '*Dupixent should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus*'. The *ETFAD* recommends not using dupilumab in pregnant or lactating women for the time being.

Oral antihistamines

The 2015 *ETFAD* guideline for the treatment of AD recommended that the use of oral H1 receptor blocking agents (antihistamines) should be limited to AD patients with concomitant urticaria, since antihistamines have no effect on any pruritic mediator other than histamine.[1] The EAACI/GA$_2$LEN/EDF/WAO guideline for the treatment of urticaria recommends careful use of the second-generation H1-antihistamine loratadine with possible extrapolation to desloratadine and cetirizine, whereas the use of sedating antihistamines is not recommended.[87] Up-dosing of antihistamines should be done only after careful consideration. Sedating antihistamines are used by some dermatologists and members of the *ETFAD* to increase sleep quality; yet, patients should be made aware of the long-term effects on motoric function and cognitive function, e.g. driving a car or studying.

Small-scale studies on cetirizine[121] and loratadine[122] show a good safety profile when oral antihistamines are used in pregnant AD patients.

It is the recommendation of the *ETFAD* that antihistamines in pregnant women with AD may be used if clinically indicated, while being aware of their limited efficacy. Loratadine should preferentially be used because of the large clinical experience with this substance. Sedating antihistamines should be used only on very strict indications and after weighing the benefit/risk ration carefully.

Treatment of AD in men wishing to father a child

Considerations of proper treatment in men who desire to father a child should generally address whether or not the administered drug decreases male fertility or is secreted in the seminal fluid and has teratogenic effects.

Topical treatments

In general, the literature on this subject is very sparse. It is the recommendation of the ETFAD that topical AD therapies in men wishing to father a child can be used without concern according to the general guidelines and the ETFAD position paper.

Systemic treatments

In a recent critical appraisal of the literature on pregnancy outcomes after paternal exposure to immunosuppressive drugs,[6] the relationship is deemed to be unclear. Most of the studies show no relationship; however, from a pharmacokinetic point of view, the drugs may be in the seminal fluid and affect spermatogenesis. The limited clinical evidence and *ETFAD* recommendation are presented here.

Systemic corticosteroids

Women	Preconceptive	May be used as rescue therapy, or as bridging until effect of other systemic or biological medicaments
	Pregnant	May be used as rescue therapy, or for short periods of time (2–3 weeks), not exceeding 0.5 mg/kg/day. Prednisolone is the preferred drug
	Lactating	May be used as rescue therapy
Men	Preconceptive	No restrictions compared to the ETFAD position paper on atopic dermatitis

The use of systemic corticosteroids in men wishing to father a child is not contraindicated, and use should follow the general guidelines for the treatment of AD.[1,12]

Methotrexate

In a recent consensus paper from Denmark on the treatment of psoriasis, the authors concluded that there is not ample evidence of potential teratogenic effects of MTX (5 mg–25 mg/week) when given to the future father of the child.[110] However, the authors adhered to the recommendation of the European S3-guideline on systemic treatment of psoriasis vulgaris and recommended a 3-month MTX pause prior to conception.[123] Anecdotal reports on male oligospermia during MTX treatment have been published.[111] Follow-up studies on low-dose MTX treatment in men have, however, not been able to show any increased incidence in birth malformation in children of fathers treated with MTX at the time of conception,[124] which was also the case in a recent nationwide Danish registry study.[125]

The recommendation of the *ETFAD* is that caution should be taken. According to the current recommendation of the European S3 Guidelines for the treatment of psoriasis vulgaris with MTX, the drug should be paused 3 months prior to the desired time of conception. However, (inadvertent) exposure beyond this time does not justify termination of pregnancy, because there is no evidence of male teratogenicity.

Azathioprine

A recent meta-analysis of 14 human observational studies including a total of 975 births showed that 53 were born with congenital abnormalities following paternal exposure to AZA during conception. The studies predominantly included patients with kidney transplants, inflammatory bowel disease and systemic lupus erythematosus. In total, 5.4% of the children were

born with congenital abnormalities compared with 3% of the background population (non-significant difference).[126] The authors concluded that larger studies are needed to evaluate the putative effect on children fathered by men on AZA treatment and that evidence so far is unclear. In a Danish population study of 1246 children fathered by men treated with AZA at the time of conception, no significant increase in malformations could be detected.[125]

According to the FDA label, there is no contraindication for the use of azathioprine in men. The *ETFAD* recommends that azathioprine be used in severe cases of AD patients wishing to father a child where other therapies have failed or are contraindicated.

Cyclosporine A

A recent review paper including 17 human studies concluded that when cyclosporine A is given at the lowest possible dosage, normal fertility can be achieved.[127] CyA is safe to use in men wishing to father a child, as has been previously concluded.[128] In a Danish registry study, the same result was found in 247 children conceived by men treated with CyA.[125] Neither the FDA nor the EMA have issued contraindications for the use of CyA in men wishing to father a child. It is the recommendation of the *ETFAD* that CyA may be used in the treatment of AD in men at the time of conception if other treatments fail or are contraindicated.

Mycophenolate mofetil

Information on the use of MMF by men and any associated teratogenicity is limited. In a recent registry study from Norway which included 230 men with kidney transplants, immunosuppressed with MMF and fathering 350 children in the period 1995–2015, no increased risk of malformation was observed in the children.[129] The authors concluded that MMF can be safely used in men at the time of conception. However, according to the EMA label, it is advised that men treated with mycophenolate mofetil use a condom during and for at least 90 days after treatment cessation of MMF.

It is the recommendation of the *ETFAD* that men of reproductive potential should be made aware of the theoretical risk of teratogenicity if fathering a child while being treated with MMF and be advised to use condoms as contraception during and for at least 90 days after cessation of MMF therapy. However, failure of contraception during this time does not justify termination of pregnancy because there is no evidence of male teratogenicity.

Dupilumab

There is no literature on male AD patients treated with dupilumab who wish to father a child. Theoretically, there could be a transfer of an unknown percentage of antibodies to the seminal fluid. The potential teratogenicity of dupilumab and its possible interference with male fertility are unknown.

Unplanned pregnancy during systemic treatment

Women

It is of the outmost importance that when systemic treatment is prescribed, the patient should be well-informed about the consequences of pregnancy during treatment.

It is the recommendation of the *ETFAD* that when initiating treatment with MTX and MMF, women of childbearing potential should also start efficient contraceptive treatment. If a woman gets pregnant, she should immediately cease systemic treatment, intensify topical treatment and be referred to an obstetrician and to a Teratology Information Centre for individual risk assessment. The AD should be treated according to current guidelines and position papers, and the outcome should be documented in registries such as the national AD treatment registries that belong to international TREAT (TREatment of ATopic eczema registry taskforce (https://treat-registry-taskforce.org).[130]

Summary and conclusion

Treatment of AD should generally follow a 'safety first' approach with effective treatment options rather than avoiding nearly all possible treatment modalities. Generous use of emollients should always be the basis of AD treatment, which also applies for pregnant women. Topical use of class II steroids, such as prednicarbate, is a safe and moderately effective treatment option. TCI, preferentially tacrolimus, are recommended as a safe alternative. The next step in treatment is the addition of UV light treatment to TCS, with narrow-band UVB-311 nm being the treatment of first choice. Moderate sun exposure may also be a helpful and readily accepted regimen for many women. Systemic treatment may be given with strict indication, but is rarely needed in fully compliant patients. CyA and SCS should be discussed with the patients as the first systemic treatment options. Azathioprine may be continued as a treatment in women who get pregnant during this therapy if no other options are available. The data on the use and outcome of systemic therapy used during pregnancy are very sparse, and the *ETFAD* recommends that future registries following the TREAT guidelines also capture these data.

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