REVIEW ARTICLE



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Systemic anti-inflammatory treatment of atopic dermatitis during conception, pregnancy and breastfeeding: Interdisciplinary expert consensus in Northern Europe

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Abstract

Treating atopic dermatitis (AD) in pregnant or breastfeeding women, and in women and men with AD aspiring to be parents is difficult and characterized by uncertainty, as evidence to inform decision-making on systemic anti-inflammatory treatment is limited. This project mapped consensus across dermatologists, obstetricians and patients in Northwestern Europe to build practical advice for managing AD with systemic anti-inflammatory treatment in men and women of reproductive age. Twenty-one individuals (sixteen dermatologists, two obstetricians and three patients) participated in a two-round Delphi process. Full consensus was reached on 32 statements, partial consensus on four statements and no consensus on four statements. Cyclosporine A was the first-choice long-term systemic AD treatment for women preconception, during pregnancy and when breastfeeding, with short-course prednisolone for flare management. No consensus was reached on second-choice systemics

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preconception or during pregnancy, although during breastfeeding dupilumab and azathioprine were deemed suitable. It may be appropriate to discuss continuing an existing systemic AD medication with a woman if it provides good disease control and its benefits in pregnancy outweigh its risks. Janus kinase (JAK) inhibitors, methotrexate and mycophenolate mofetil should be avoided by women during preconception, pregnancy and breastfeeding, with medication-specific washout periods advised. For men preconception: cyclosporine A, azathioprine, dupilumab and corticosteroids are appropriate; a 3-month washout prior to conception is desirable for methotrexate and mycophenolate mofetil; there was no consensus on JAK inhibitors. Patient and clinician education on appropriate (and inappropriate) AD treatments for use in pregnancy is vital. A shared-care framework for interdisciplinary management of AD patients is advocated and outlined. This consensus provides interdisciplinary clinical guidance to clinicians who care for patients with AD before, during and after pregnancy. While systemic AD medications are used uncommonly in this patient group, considerations in this article may help patients with severe refractory AD.

INTRODUCTION

Atopic dermatitis (AD) is the most common skin disease in pregnancy¹ and follows an unpredictable course; symptom worsening has been reported in 52%² and 61%³ of women, while improvements reported in around 20%.⁴ For the rest, symptoms remain unchanged.

Treating future parents of both sexes, and pregnant or breastfeeding women with AD is challenging, as no large studies on the effects of treatment during preconception, pregnancy and lactation exist or on their safety for the unborn child. Some attention has been paid to the effects of anti-inflammatory drugs on female fertility, but less to male fertility and potential teratogenicity following paternal exposure, so multiple data gaps exist. Furthermore, patients often wish to avoid taking any medication during pregnancy or before conception due to safety concerns equally, clinicians and pharmacists are often reluctant to prescribe or advise medications during pregnancy.

In 2019, the European Task Force on Atopic Dermatitis (ETFAD) published a position paper¹ recommending AD treatment in pregnancy should generally follow a 'safety first' approach using effective medications associated with low risk, rather than avoiding all treatments.¹ The ETFAD advocates optimising non-systemic treatment, including daily emollients, intermittent use of most topical corticosteroids and calcineurin inhibitors, and ultraviolet B for pregnant and lactating women. If systemic treatment is needed, cyclosporine A, azathioprine and short courses of systemic corticosteroids are justifiable based on evidence in patients with organ transplants.¹

The ETFAD position paper, like other guidelines,^{7–9} reinforces the importance of joint decision-making with patients. Further, the benefit of collaboration with obstetricians or a broader multidisciplinary team, especially when considering biologics, is advocated. ^{1,4,7,10} How this is put into practice is, however, unspecified.

This project convened dermatologists, obstetricians and patients from North-western Europe to develop practical advice for treating AD in men and women of reproductive age. It supplements, not replaces, published clinical guidelines. ^{1,7,9,11} The consensus is based on expert opinion and is intended to help clinicians make treatment decisions when high-quality experimental evidence is lacking.

MATERIALS AND METHODS

The project explored clinical collaborations and joint decision-making and considered systemic anti-inflammatory treatment during pregnancy and breastfeeding. Prepregnancy planning for both sexes was also considered. AD of any severity was discussed, with a focus on moderate to severe disease in pregnant women. Discussion of topical treatments, antihistamines, antibiotics and atopic eruptions of pregnancy were outside scope.

Delphi methodology was used to explore consensus. Delphi is a recognized consensus approach useful when data are limited, and expert opinion is important in shaping judgements. ^{12–15} A two-round Delphi was conducted using online surveys.

Definitions of consensus

Responses to survey statements were captured via a 9-point Likert scale; from 1 ('Strongly disagree') to 9 ('Strongly agree'). Experts could give no answer if the question was outside their expertise. Experts were encouraged to add free text to explain their response to support statement modification between rounds.

Consensus was defined a priori if ≥75% of responses scored 7, 8 or 9 ('Agree' to 'Strongly agree'), as in similar projects. Partial consensus occurred if some—but not all—parts of a multi-part question reached consensus.

Participants

The experts were 16 dermatologists experienced in managing AD, two obstetricians and three patient representatives. Clinicians were selected for their practical expertise, publishing records, national and regional standing and interests. A subset of eight experts formed a steering committee (SC).

Meeting facilitation, data analysis and project management were conducted by an impartial Delphi facilitator, assisted by a medical writer. The sponsor abstained from discussions and had no input on the surveys, Delphi, or consensus. The views and opinions reported are the authors' alone.

Survey development

The SC agreed on project scope, target patients and topics for consideration. To support this, a comprehensive gap analysis of the literature, including guidelines ^{1,7,9,11} and literature appraisals, ^{4,10} was done to identify areas where best practices are unclear; this project focused on the gaps. Additionally, a search for articles published after the ETFAD guideline was submitted for publication (January 2018) aimed to capture recent data. The gap analysis was provided to all experts as part of the Delphi surveys. Draft statements were developed, refined, and agreed by the SC.

The SC reviewed the Round 1 result and developed the Round 2 survey. A virtual results meeting allowed experts to contextualize their opinions (Figure 1).

RESULTS

Across the two rounds, 32 statements reached full consensus (Figure 1).

Pre-pregnancy planning and conception

Accurate information and education are vital for patients with AD

Research is limited on the educational needs of patients with AD and their physicians; however, data from related conditions highlight the need for better education. For example, a survey of 141 US women with psoriasis—a chronic condition with treatments overlapping with AD—revealed a lack of awareness among patients on its management before and during pregnancy. Sixty-five percent of interviewees who became pregnant stopped the treatment they were taking, with nearly one-quarter taking this decision themselves and one-third citing misinformation regarding the treatment's compatibility with pregnancy. Again, although AD-specific information is lacking, reasons for physicians' undertreatment of other chronic inflammatory diseases, including psoriasis and rheumatoid arthritis, include poor guidelines knowledge, medication safety fears for mother and baby and

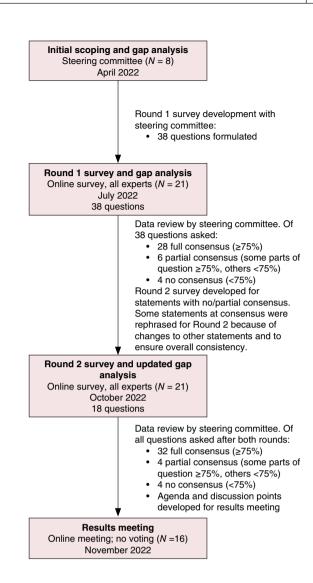


FIGURE 1 Development of consensus through the Delphi rounds.

little experience of treating pregnant women. 6,23 Indeed, an obstetrician in our project explained that, in her experience, patients are often instructed by their general practitioner or nurse to stop all treatments when trying to conceive, and she suggested education is thus needed for primary care practitioners, pharmacists, and midwives too.

Our experts almost unanimously agreed that wideranging patient education, including what to expect with AD in pregnancy, which treatments are appropriate or inappropriate, and when and how to seek advice, is important for men and women wishing to conceive. Such advice is best given individually and in collaboration with an obstetrician¹; a view echoed by our patient representatives (Table 1).

Our obstetricians noted that, in some settings, communication between obstetrics and other disciplines is common, especially for those managing diseases where systemic treatments are used, such as gastroenterology and rheumatology. Patients with AD needing systemics would similarly benefit from such interdisciplinary collaboration between obstetricians and dermatologists, and perhaps with fertility centres if

TABLE 1 Pre-pregnancy education for patients with atopic dermatitis.

			Likert score, %			
	Statement	Status	1-3	4-6	7-9	Respondents, n
1	All women with AD who are planning pregnancy should receive ed	ducation on:				
	(a) the potential AD disease course during pregnancy	Consensus (Round 2)	0	5	95	21
	(b) the risk of uncontrolled AD to the mother	Consensus (Round 2)	5	5	90	21
	(c) the AD medication that is safe to use prepregnancy	Consensus (Round 2)	0	0	100	21
	(d) when, prior to conception, to stop AD treatments that are unsafe in pregnancy	Consensus (Round 2)	0	0	100	21
	(e) what to do if a woman becomes pregnant while receiving AD treatment that is unsafe to use during pregnancy	Consensus (Round 2)	5	0	95	21
	(f) where to find advice relating to AD treatment during pregnancy	Consensus (Round 2)	0	0	100	21

Note: Green: Consensus was reached regarding the question in the group of experts involved in the Delphi process.

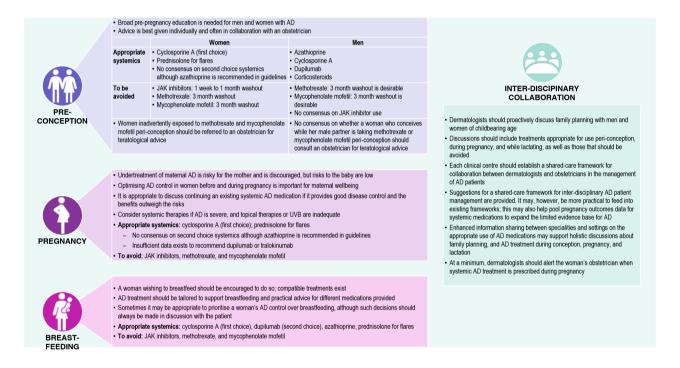


FIGURE 2 Key consensus recommendations. AD, atopic dermatitis; JAK, Janus-activated kinase; UVB, ultraviolet B.

appropriate. Given the rapid development of systemics for AD and the increasing willingness of dermatologists to use them, such collaborations are becoming more important.

Cyclosporine A is the first choice for women preconception; second choices were not agreed

In common with the ETFAD recommendations, our experts agreed cyclosporine A is the first-choice systemic in women before and during conception, and prednisolone is appropriate for short-term flare management (Figure 2; Table S1). However, there was no consensus on second-choice systemics for long-term AD control preconception in women. Our experts thought this problematic, as conception can take multiple years and the burden of untreated AD

can be high, meaning women unable to take cyclosporine A need effective alternatives. Most experts felt azathioprine was appropriate; interestingly, all obstetricians favoured azathioprine, while some dermatologists were hesitant. We suggest this reflects differences in perspective: obstetricians see azathioprine used for other indications without adverse consequences, while in most countries, dermatologists use it infrequently for AD, and even less so preconception.

JAK inhibitors, methotrexate and mycophenolate mofetil should be avoided for women preconception

In common with guidelines, the experts all agreed that women should avoid JAK inhibitors, methotrexate and

mycophenolate mofetil preconception, with washout periods largely aligned with guidelines. The exception was methotrexate: our experts recommended a shorter washout than ETFAD¹ (3 vs. 6 months; Figure 2).

There was unanimous consensus that women inadvertently exposed to methotrexate, mycophenolate mofetil or JAK inhibitors preconception should be referred to an obstetrician for teratological advice, or to other services offering this (Table S2). For example, in Finland, patients and healthcare providers can contact the Teratological Information Service for information and support.

Azathioprine, cyclosporine A, dupilumab and systemic corticosteroids are appropriate for men preconception

Data from non-AD indications suggest that azathioprine and cyclosporine A are compatible with paternal exposure, ^{24,25} although some data suggest azathioprine may reduce sperm motility or induce oligospermia. ^{26–28} Similarly, data are mixed on the effects of high-dose glucocorticoids on male fertility. ²⁹ Our experts agreed all these drugs are appropriate for men preconception, although some expressed concerns around azathioprine and suggested close follow-up in case of fertility concerns would be needed (Table 2).

Although no information exists on the effects of either dupilumab or tralokinumab on male fertility, the experts largely agreed dupilumab could be used, but reached no consensus for tralokinumab. Given their similar modes of action, the experts suggest these drugs likely have a similar safety profile but recommend dupilumab for now as it has been available for longer.

For men preconception, a washout period for methotrexate and mycophenolate mofetil is desirable

Experts largely agreed that a 3-month washout period for methotrexate and mycophenolate mofetil was desirable, with many suggesting just 1 month, but evidence suggests that even this may be unnecessary (Table 2). Historically, literature regarding paternal exposure to both agents has been conflicting, ^{24,26} but recent evidence for methotrexate is more reassuring. ²⁹⁻³¹ While the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommend a washout period (3 and 6 months, respectively) before conception attempts begin for men using methotrexate, the American College of Rheumatology changed their recommendation in 2020 to 'conditionally recommend continuing' methotrexate in men wishing to become fathers.³² Some of our experts suggested that stopping these therapies may reduce AD control, which is not proportionate to the hypothetical risks of teratogenicity.

TABLE 2 Prepregnancy systemic atopic dermatitis treatments appropriate for men.

			Likert score, %					
	Statement	Status	1-3	4-6	7-9	Respondents, n		
10	The systemic anti-inflammatory medications that can be used by MEN with AD prior to and during conception are (in alphabetical order):							
	(a) Azathioprine	Consensus (Round 2)	12	13	75	16		
	(b) Cyclosporine A	Consensus (Round 2)	0	0	100	18		
	(c) Dupilumab	Consensus (Round 2)	11	11	78	18		
	(d) JAK inhibitors (abrocitinib, baricitinib, upadacitinib)	No consensus	33	17	50	18		
	(e) Systemic corticosteroids	Consensus (Round 2)	6	6	89	18		
	(f) Tralokinumab	No consensus	11	22	67	16		
11	A washout period of 3 months prior to conception is desirable for MEN who are taking:							
	(a) Methotrexate	Consensus (Round 2)	6	17	78	18		
	(b) Mycophenolate mofetil	Consensus (Round 2)	6	6	89	18		
12	A woman who conceives while her male partner has been taking methotrexate for AD in the 3 months prior to conception does not need to consult an obstetrician for teratological advice	No consensus	28	6	67	18		
13	A woman who conceives while her male partner has been taking mycophenolate mofetil for AD in the 3 months prior to cwwonception does not need to consult an obstetrician for teratological advice	No consensus	30	12	59	17		

Note: Green: Consensus was reached regarding the question in the group of experts involved in the Delphi process. Pale red: No consensus was reached regarding the question in the group of experts involved in the Delphi process.

Experts reached no consensus on JAK inhibitors in men wishing to conceive

Data on JAK inhibitors are scarce, and the experts reached no consensus on their use in men wishing to conceive (Table 2). One expert stated concerns over testicular toxicity, evidenced by the recent FDA rejection of filgotinib for rheumatoid arthritis on these grounds.³³ The information on testicular toxicity for other JAK inhibitors is inconclusive, although has not been seen for baricitinib or tofacitinib in clinical use.^{34,35}

AD and its treatment during pregnancy

Undertreatment is risky for the mother and is discouraged, but risks to the baby are low

Stress during pregnancy may exacerbate the mother's AD symptoms and reduce her quality of life. While our experts agree AD undertreatment is detrimental to the mother's health, little robust evidence links maternal stress to adverse outcomes in her child and studies have conflicting findings. For example, a Danish population study showed the risks associated with maternal AD in pregnancy include premature rupture of membranes and staphylococcal neonatal septicaemia, although the absolute risks were very low.^{9,36} Conversely, a 2021 Japanese study found no association between maternal AD and threatened preterm labour. 37 Reflecting this conflicting evidence base, our experts reached no consensus on whether AD and associated stress and anxiety can pose risks to the offspring, although most agreed that optimising the mother's AD control could be of some benefit to the baby (Table 3).

Consider systemics if AD is severe and topical therapies or UVB are inadequate

All our experts agreed systemic therapy is appropriate for severe AD inadequately controlled by topical therapies or UVB therapy (Table 4). They also agreed it is appropriate to discuss the continuation of a woman's existing systemic AD medication if it provides good disease control and benefits outweigh potential risks.

Our experts reached the same consensus as the ETFAD,¹ agreeing that cyclosporine A should be the first choice for pregnant women whose AD is uncontrolled with non-systemic treatments, and that prednisolone (≤0.5 mg/kg/day) can be used for flares (Figure 2; Table S3). As with preconception choices, our experts reached no consensus on appropriate second-line systemics during pregnancy, and for the same reasons. Over 70% of experts—including all obstetricians—suggested azathioprine, but others disagreed on account of limited experience in pregnant women with AD, or their own limited use of azathioprine in AD generally.

Although it did not reach consensus, there was discussion of using low-dose corticosteroids for the entire duration of a woman's pregnancy because the risk: benefit ratio during pregnancy may differ from that outside of pregnancy. Indeed low-dose corticosteroid use is supported by safety data from other indications, ³⁸ and our expert obstetrician considered it unconcerning.

Insufficient data exist to recommend dupilumab or tralokinumab in pregnancy

The experts reached no consensus on dupilumab or tralokinumab, citing the lack of safety data in pregnant women

TABLE 3 Atopic dermatitis control and maternal well-being before and during pregnancy.

			Likert score, %			
	Statement	Status	1-3	4-6	7-9	Respondents, n
14	It should be recognized that even women with mild or well-controlled AD may experience worsening of AD during pregnancy, although the risk is greatest for patients with more severe AD prepregnancy	Consensus (Round 1)	0	0	100	21
15	It should be recognized that AD symptoms during pregnancy expose the w	oman to stress and anxiet	y, whicl	h may:		
	(a) exacerbate maternal AD	Consensus (Round 2)	0	10	90	20
	(b) reduce the quality of life of the mother	Consensus (Round 2)	0	0	100	19
	(c) increase the risk of AD in the offspring	No consensus	30	36	35	17
16	There should be greater awareness of the risks of AD undertreatment to the mother, as well as wider recognition that some effective AD treatments are safe and necessary in pregnancy	Consensus (Round 2)	0	0	100	21
17	Optimising AD control in women prior to conception and during pregnancy is important to protect the mother	Consensus (Round 2)	5	0	95	21
18	The risks to the baby of uncontrolled maternal AD are low. Nevertheless, optimising AD control in the mother during pregnancy could be of some benefit to the baby	Consensus (Round 2)	5	10	85	20

Note: Green: Consensus was reached regarding the question in the group of experts involved in the Delphi process. Pale red: No consensus was reached regarding the question in the group of experts involved in the Delphi process.

TABLE 4 General considerations for atopic dermatitis control during pregnancy.

			Likert sc			
	Statement	Status	1-3	4-6	7-9	Respondents, n
19	During pregnancy, AD should be primarily controlled with topical corticosteroids, topical calcineurin inhibitors and UVB therapy and adherence should be optimized	Consensus (Round 1)	0	0	100	18
20	Systemic treatment during pregnancy should be considered when the patient has severe AD (such as severe itch, sleep loss, and impaired DLQI) that is inadequately controlled by recommended topical treatments, UVB therapy, and patient education	Consensus (Round 1)	0	0	100	18
21	If a pregnant woman's severe AD is well controlled on her current systemic AD medication, it is appropriate to discuss with her the continuation of her existing systemic therapy if the benefits outweigh the potential risks	Consensus (Round 1)	0	0	100	18

Note: Green: Consensus was reached regarding the question in the group of experts involved in the Delphi process.

TABLE 5 Considerations for atopic dermatitis treatment during breastfeeding.

			Likert score, %			
	Statement	Status	1-3	4-6	7-9	Respondents, n
26	A woman with AD who wishes to breastfeed should be encouraged to do so; her AD treatment should be tailored to accommodate this	Consensus (Round 1)	0	0	100	21
27	For a woman with severe AD who does not have a strong desire to breastfeed and is willing to use alternatives, it is appropriate for dermatologists to advocate prioritising her AD control using systemic therapy over breastfeeding, as part of shared decision-making with the patient	Consensus (Round 2)	5	10	85	20
28	Active treatment of nipple eczema should be encouraged to enable breastfeeding	Consensus (Round 1)	0	0	100	21
29	Topical corticosteroids (or topical calcineurin inhibitors) should be applied to the nipple immediately after breastfeeding, and the nipple should then be cleaned gently prior to the next breastfeed to avoid exposing the newborn to topical corticosteroids or calcineurin inhibitors	Consensus (Round 1)	0	0	100	19

Note: Green: Consensus was reached regarding the question in the group of experts involved in the Delphi process.

(Table S3). This aligns with the ETFAD position¹; their guidelines contain no information on tralokinumab because Phase 3 data were unavailable when they were drafted.

No strong evidence exists on biologics for AD in pregnancy, only case reports^{35,39,40} and a database review⁴¹ on dupilumab; all so far conclude dupilumab appears safe during pregnancy. Patient representatives suggested this is an area where anonymized registry data could help fill knowledge gaps, and that patients would be willing to participate in such initiatives.

Breastfeeding

Systemic treatment options exist for women with AD wishing to breastfeed

Breastfeeding is advocated by the World Health Organization, 42 but this advice may not suit all families,

and excellent alternatives are available should a woman decide not to breastfeed. Our experts agreed that a woman wishing to breastfeed should be encouraged to do so, and that treatments compatible with breastfeeding exist. The experts agreed that sometimes it may be appropriate to prioritize AD control over breastfeeding, although such decisions should always be made together with the patient (Table 5).

Cyclosporine A is the first-choice long-term therapy during breastfeeding

Our experts again recommended cyclosporine A as the first-choice long-term systemic, and prednisolone for flares. Most agreed dupilumab is an appropriate second choice (Figure 2; Table S4). Preliminary evidence indicates dupilumab may be safe during breastfeeding, even if low

doses are secreted into breastmilk. When ingested it is likely destroyed in the infant's gastrointestinal tract. The LactMed* database advises caution with dupilumab use during breastfeeding, especially while nursing a newborn or preterm infant, until more evidence is available. No information is yet available for tralokinumab, but the same advice is given as for dupilumab. 43

While most experts agreed azathioprine may be better avoided due to difficulties with timing doses relative to breastfeeding, one obstetrician suggested that experience from patients with rheumatological conditions shows azathioprine during breastfeeding carries no significant concerns. 44-46

JAK inhibitors are contraindicated in pregnancy and breastfeeding due to teratogenicity in animals, and the experts unanimously agreed (Table S4). One highlighted that women are at an elevated risk of venous thromboembolism in pregnancy and early post-partum; therefore, even should a woman decide not to breastfeed, JAK inhibitors may still be inappropriate for post-partum use.

Clinical collaborations and joint decision-making

Dermatologists should proactively discuss family planning with AD patients of childbearing age

All our experts advocate positive, proactive family-planning discussions that include men and women, and which discuss the treatments appropriate for use preconception, during pregnancy and while lactating, not just those to avoid (Figure 2; Table S5). Although national differences exist, patients with mild-to-moderate AD are generally managed in primary care: the most likely setting in which family planning is discussed. Those with more severe AD requiring systemic medication tend to be managed in secondary or tertiary care by dermatologists, where family planning may not be considered in treatment plans. Obstetricians and gynaecologists see mostly women with complex pregnancies or comorbid conditions, or when the health of the foetus must be considered, and uncommonly encounter patients for whom early and effective AD treatment may be beneficial. Enhanced information sharing between these specialities and settings may support holistic discussions about family planning, and AD treatment during conception, pregnancy and lactation.

Shared-care frameworks could improve inter-specialty collaborations

The experts agreed a shared-care framework between dermatologists and obstetricians would be valuable, especially as use of systemics is becoming widespread and the need for effective communication more important (Table 6).

Cross-specialty communications are common between obstetricians and rheumatologists, cardiologists and gastroenterologists, but less common between obstetricians and dermatologists. We give practical advice for shared-care arrangements, although suggest incorporating dermatology into existing shared-care frameworks to reduce administrative burden, especially in smaller units. Feeding into existing frameworks may help pool pregnancy data for systemic medications—many of which are used for other indications—and may expand the limited evidence base for AD.

DISCUSSION

The impact of AD and its treatments on teratogenicity, fertility, pregnancy and breastfeeding outcomes are considerations for both sexes in all stages of family planning, as is the need for continuous disease control to safeguard the patient's well-being. These considerations are best discussed proactively with patients—male and female—and information shared among all specialties involved in their care. It is vital that patients and clinicians are educated on which treatments are safe to use in pregnancy, not just those that are not, to reduce undertreatment or the use of unsafe therapies. Further, proactive information sharing between specialties is needed to fill the data gaps owing to the lack of empirical data in these patients.

This consensus captures the opinions of dermatologists, obstetricians and patients on how to enhance AD management in patients of childbearing age needing systemic anti-inflammatory treatment. The key consensus recommendations are shown in Figure 2.

This consensus aligns with existing guidelines but offers additional opinions and ideas, particularly around interdisciplinary collaboration between dermatologists and obstetricians, as well as joint decision-making with patients. With such limited data, embracing shared-care frameworks that could enhance patient care and offer a way of collecting additional patient data is desirable.

The authors note some limitations. First, our group was small and weighted with dermatologists, as these are most likely to prescribe systemics for patients of childbearing age with AD. Second, sometimes the views of dermatologists and obstetricians diverged. We suggest reasons for this divergence but given the small numbers, especially of obstetricians, we must be cautious in our conclusions on these differences. Third, we acknowledge national and regional differences limit the applicability of our suggestions to this small group of related countries in Northwestern Europe. Lastly, the views are based on the opinions of a small group of physicians in the same geographical region. While highly experienced, their opinions cannot supplant well-conducted research. Frustratingly, this is presently lacking; however, improving cross-specialty collaborations could help synthesize information and build evidence to support future decision-making.

TABLE 6 Considerations for implementing shared-care frameworks to enhance the care of patients of childbearing age with atopic dermatitis.

			Likert score, %			
	Statement	Status	1-3	4-6	7–9	Respondents, n
37	Each hospital or clinical centre should establish a shared-care framework for collaboration between dermatologists and obstetricians on the use of immunomodulatory/immunosuppressive treatments, including in the management of patients with moderate to severe AD who wish to conceive, or who are pregnant or breastfeeding	Consensus (Round 1)	0	5	95	21
38	This shared-care framework:					
	(a) should be agreed and written by local specialist dermatologists and obstetricians taking a lead on immune-dermatology and AD in pregnancy	Consensus (Round 1)	0	10	90	21
	(b) should identify the circumstances in which dermatologists should consult or refer AD patients to an obstetrician	Consensus (Round 1)	0	5	95	21
	(c) should identify the key staff in different departments who have expertise in managing AD in pregnancy	Consensus (Round 1)	0	10	90	21
	(d) should be communicated to all healthcare professionals managing women with AD during pregnancy	Consensus (Round 1)	0	0	100	21
	(e) should be reviewed and updated regularly to keep abreast of changes in clinical practice and treatment recommendations	Consensus (Round 1)	0	0	100	21
	(f) should include consistent approaches to patient education on AD in pregnancy	Consensus (Round 1)	0	10	90	21
	(g) should provide consistent guidance on safe and unsafe treatment options	Consensus (Round 1)	0	0	100	21
	(h) should provide information on preconception washout periods of AD treatments, where necessary	Consensus (Round 1)	0	0	100	21
	(i) should ensure data on AD and pregnancy outcomes are recorded for the purpose of building additional knowledge	Consensus (Round 1)	0	10	90	21
39	Patients with the most severe AD should be given a patient education leaflet outlining the benefits and risks of different AD treatments to aid effective shared care decision-making during conception, pregnancy and while breastfeeding	Consensus (Round 1)	0	0	100	21
40	At a minimum, dermatologists should alert the woman's obstetrician when systemic AD treatment is prescribed during pregnancy	Consensus (Round 1)	0	5	95	20

Note: Green: Consensus was reached regarding the question in the group of experts involved in the Delphi process.

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CONFLICT OF INTEREST STATEMENT

AHL is a consultant for AbbVie and Sanofi. AS is a consultant, speaker and/or expert for AbbVie, Leo Pharma, Galderma, Sanofi, Lilly. She has received support for attending meetings from AbbVie. BD is a consultant, advisor and/ or speaker for Pfizer, Lilly, AbbVie, Stallergènes Greer, Leo Pharma, Janssen, Novartis. She has received support for attending a meeting from AbbVie. CV is a consultant, speaker and/or advisor for Sanofi, Almirall, Leo Pharma, Novartis, Lilly, Astra Zeneca, Pierre Fabre, Meda. He has received support for attending meetings from Sanofi. EW is a consultant and/or speaker for AbbVie, Leo Pharma, Orion, Pfizer and Sanofi Genzyme. She has received support for attending meetings from Leo Pharma, Pfizer and Sanofi Genzyme. HL is a consultant and/or speaker for Pfizer, Eli Lilly, Galderma, AbbVie, Novartis, Leo Pharma and Janssen. She has received research grants from Pfizer. IK is a consultant and/or speaker for, and received support for attending meetings from, Sanofi and AbbVie. JE has been a consultant and/or speaker for Sanofi, Pfizer, Leo Pharma, Novartis, AstraZeneca, Almirall,

Boehringer Ingelheim, GSK, AbbVie, Lilly, Galderma, Takeda and CSL Vifor. He has received support for attending meetings from Stallergènes Greer. JG is a consultant and/or speaker for AbbVie, Almirall, Leo Pharma, Janssen, Lilly, Pfizer and has received support for attending meetings from AbbVie, Almirall, Janssen, Leo Pharma. He has received grants from AbbVie, Almirall, Leo Pharma, Lilly, Pfizer. JMM is a consultant or speaker for Abbvie, Boehringer, Leo Pharma, Lilly, Pfizer, Sanofi and Sidekick. JPT is an advisor and/or speaker for Sanofi Genzyme, Regeneron, Pfizer, AbbVie, Leo Pharma, OM-85, Arena, Aslan, Almirall, Coloplast, RAPT Therapeutics, Union Therapeutics. He has received grants from Pfizer, Regeneron, Sanofi Genzyme. MB has declared no conflicts of interest. MCS is an advisor for Sanofi. MD is an advisor or speaker for Leo Pharma, AbbVie, Lilly, Regeneron, Sanofi Genzyme, Pfizer, Pierre Fabre, Novartis, Almirall, Arena Pharmaceuticals, ASLAN Pharmaceuticals, Incyte and Kymab, and La Roche Posay. She has received grants from Leo Pharma, AbbVie, Lilly, Regeneron, Sanofi Genzyme and Pfizer. MdBW is a consultant, advisory board member and/or speaker for AbbVie, Almirall, Aslan, Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron and Sanofi Genzyme. MLAS is a consultant, advisory board member and/or speaker for Sanofi Genzyme, AbbVie, Lilly, Leo Pharma, Pfizer. She has received research grants from Sanofi Genzyme and Pfizer.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

This work did not involve experimentation on human participants; therefore, ethics permission was not necessary or sought.

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REFERENCES

- Vestergaard C, Wollenberg A, Barbarot S, Christen-Zaech S, Deleuran M, Spuls P, et al. European task force on atopic dermatitis position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. J Eur Acad Dermatol Venereol. 2019;33:1644–59.
- 2. Kemmett D, Tidman MJ. The influence of the menstrual cycle and pregnancy on atopic dermatitis. Br J Dermatol. 1991;125:59–61.
- 3. Cho S, Kim HJ, Oh SH, Park CO, Jung JY, Lee KH. The influence of pregnancy and menstruation on the deterioration of atopic dermatitis symptoms. Ann Dermatol. 2010;22:180–5.
- Balakirski G, Novak N. Atopic dermatitis and pregnancy. J Allergy Clin Immunol. 2022;149:1185–94.
- 5. Østensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Res Ther. 2006;8:209.
- Nelson-Piercy C, Vlaev I, Harris K, Fischer-Betz R. What factors could influence physicians' management of women of childbearing age with chronic inflammatory disease? A systematic review of

- behavioural determinants of clinical inertia. BMC Health Serv Res. 2019;19:863.
- Pfaller B, Jose Yepes-Nunez J, Agache I, Akdis CA, Alsalamah M, Bavbek S, et al. Biologicals in atopic disease in pregnancy: an EAACI position paper. Allergy. 2021;76:71–89.
- 8. Vestergaard C, Wollenberg A, Thyssen JP. European task force on atopic dermatitis (ETFAD) position paper: treatment of parental atopic dermatitis during preconception, pregnancy and lactation period. J Eur Acad Dermatol Venereol. 2020;34:426–7.
- Wollenberg A, Kinberger M, Arents B, Aszodi N, Barbarot S, Bieber T, et al. European dermatology forum. Living EuroGuiDerm Guideline for the Systemic Treatment of Atopic Eczema 2022. Available at: https://www.edf.one/home/Guidelines/EuroGuiDerm-2022.html. (last accessed June 2022).
- Heilskov S, Deleuran MS, Vestergaard C. Immunosuppressive and immunomodulating therapy for atopic dermatitis in pregnancy: an appraisal of the literature. Dermatol Ther (Heidelb). 2020;10:1215–28.
- 11. Wollenberg A, Kinberger M, Arents B, Aszodi N, Barbarot S, Bieber T, et al. Living EuroGuiDerm guideline for the systemic treatment of atopic eczema. 2022 Available at: https://guidelines.edf.one//guidelines/atopic-ezcema. (last accessed September 2022).
- Gerbens LA, Boyce AE, Wall D, Barbarot S, de Booji RJ, Deleuran M, et al. TREatment of ATopic eczema (TREAT) registry taskforce: protocol for an international Delphi exercise to identify a core set of domains and domain items for national atopic eczema registries. Trials. 2017;18:87.
- Simpson EL, Bruin-Weller M, Flohr C, Ardern-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the international eczema council. J Am Acad Dermatol. 2017;77:623–33.
- Sastre J, Baldrich ES, Armario Hita JC, Herráez L, Jáuregui I, Martín-Santiago A, et al. Consensus on the clinical approach to moderateto-severe atopic dermatitis in Spain: a Delphi survey. Dermatol Res Pract. 2020;2020:1524293.
- Remitz A, De Pità O, Mota A, Serra-Baldrich E, Vakirlis E, Kapp A. Position statement: topical calcineurin inhibitors in atopic dermatitis. J Eur Acad Dermatol Venereol. 2018;32:2074–82.
- Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, et al. Expert perspectives on management of moderateto-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. J Allergy Clin Immunol Pract. 2017;5:1519–31.
- Thyssen JP, Berents T, Bradley M, Deleuran M, Grimstad Ø, Korhonen L, et al. Clinical management of atopic dermatitis in adults: mapping of expert opinion in 4 Nordic countries using a modified Delphi process. Acta Derm Venereol. 2020;100:adv00015.
- Thyssen JP, Heegaard S, Ivert L, Remitz A, Agner T, Bruin-Weller M, et al. Management of ocular manifestations of atopic dermatitis: a consensus meeting using a modified Delphi process. Acta Derm Venereol. 2020;100:adv00264.
- Schaller M, Almeida LMC, Bewley A, Cribier B, del Rosso J, Dlova NC, et al. Recommendations for rosacea diagnosis, classification and management: update from the global ROSacea COnsensus 2019 panel. Br J Dermatol. 2020;182:1269–76.
- De Bruin-Weller M, Biedermann T, Bissonnette R, Deleuran M, Foley P, Girolomoni G, et al. Treat-to-target in atopic dermatitis: an international consensus on a set of core decision points for systemic therapies. Acta Derm Venereol. 2021;101:adv00402.
- Chan TC, Wu N-L, Wong L-S, Cho YT, Yang CY, Yu Y, et al. Taiwanese dermatological association consensus for the management of atopic dermatitis: a 2020 update. J Formos Med Assoc. 2021;120:429–42.
- Lebwohl M, Siegel M, Shankle L, Pisenti L, Yassine M, Van Vorhees
 A comprehensive survey assessing the family planning needs of women with psoriasis. Skin. 2018;2:S89.
- 23. De Simone C, Calabrese L, Balato A, Cannavò SP, Dattola A, Esposito M, et al. Psoriasis and its management in women of childbearing age: tools to increase awareness in dermatologists and patients. G Ital Dermatol Venereol. 2020;155:434–40.

 Bermas BL. Paternal safety of anti-rheumatic medications. Best Pract Res Clin Obstet Gynaecol. 2020;64:77–84.

- 25. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795–810.
- Semet M, Paci M, Saïas-Magnan J, Metzler-Guillemain C, Boissier R, Lejeune H, et al. The impact of drugs on male fertility: a review. Andrology. 2017;5:640–63.
- 27. Grosen A, Nersting J, Bungum M, Christensen LA, Schmiegelow K, Spanò M, et al. Sperm DNA integrity is unaffected by thiopurine treatment in men with inflammatory bowel disease. J Crohns Colitis. 2019;13:3–11.
- 28. Banerjee A, Scarpa M, Pathak S, Burra P, Sturniolo GC, Russo FP, et al. Inflammatory bowel disease therapies adversely affect fertility in men- a systematic review and meta-analysis. Endocr Metab Immune Disord Drug Targets. 2019;19:959–74.
- 29. Perez-Garcia LF, Dolhain R, Vorstenbosch S, Bramer W, van Puijenbroek E, Hazes JMW, et al. The effect of paternal exposure to immunosuppressive drugs on sexual function, reproductive hormones, fertility, pregnancy and offspring outcomes: a systematic review. Hum Reprod Update. 2020;26:961–1001.
- 30. Grosen A, Bellaguarda E, Nersting J, Hvas CL, Liljeqvist-Soltic I, Stein A, et al. Low-dose methotrexate therapy does not affect semen parameters and sperm DNA. Inflamm Bowel Dis. 2022;28:1012–8.
- 31. Perez-Garcia LF, Röder E, Van Adrichem R, van Koppen LJK, Zirkzee E, Van Doorn M, et al. What is the effect of methotrexate on semen parameters of men diagnosed with immune-mediated diseases? Results of a prospective cohort study (iFAME-MTX). Ann Rheum Dis. 2022;81:84.
- Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. Arthritis Rheumatol. 2020;72:529–56.
- 33. The Lancet Rheumatology. JAK inhibitors: fate in doubt for rheumatoid arthritis? Lancet Rheumatol. 2021;3:e161.
- 34. Chapin RE, Ball DJ, Radi ZA, Kumpf SW, Koza-Taylor PH, Potter DM, et al. Effects of the Janus kinase inhibitor, tofacitinib, on testicular Leydig cell hyperplasia and adenoma in rats, and on prolactin signaling in cultured primary rat Leydig cells. Toxicol Sci. 2017;155:148–56.
- 35. Bosma A, Gerbens L, Middelkamp-Hup M, Spuls P. Paternal and maternal use of dupilumab in patients with atopic dermatitis: a case series. Clin Exp Dermatol. 2021;46:1089–92.
- Hamann CR, Egeberg A, Wollenberg A, Gislason G, Skov L, Thyssen JP. Pregnancy complications, treatment characteristics and birth outcomes in women with atopic dermatitis in Denmark. J Eur Acad Dermatol Venereol. 2019;33:577–87.
- 37. Saito-Abe M, Yamamoto-Hanada K, Pak K, Sato M, Irahara M, Mezawa H, et al. Association of maternal history of allergic features

- with preterm pregnancy outcomes in the Japan environment and children's study. Int Arch Allergy Immunol. 2021;182:650–62.
- 38. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68:s1–s106.
- Akhtar NH, Khosravi-Hafshejani T, Akhtar D, Dhadwal G, Kanani A. The use of dupilumab in severe atopic dermatitis during pregnancy: a case report. Allergy Asthma Clin Immunol. 2022;18:9.
- 40. Lobo Y, Lee RC, Spelman L. Atopic dermatitis treated safely with dupilumab during pregnancy: a case report and review of the literature. Case Rep Dermatol. 2021;13:248–56.
- 41. Khamisy-Farah R, Damiani G, Kong JD, Wu JH, Bragazzi NL. Safety profile of Dupilumab during pregnancy: a data mining and disproportionality analysis of over 37,000 reports from the WHO individual case safety reporting database (VigiBase). Eur Rev Med Pharmacol Sci. 2021;25:5448–51.
- 42. WHO. *Breastfeeding*. 2021. Available at: https://www.who.int/healthtopics/breastfeeding#tab=tab_1. (last accessed June 2022).
- US National Library of Medicine. Drugs and Lactation Database (LactMed). 2022. Available at: https://www.ncbi.nlm.nih.gov/books/ NBK576870/. (last accessed September 2022).
- 44. Singh M, Qualie J, Currie A, Howarth ES, Khare MM. Is breastfeeding safe with azathioprine? Obstet Med. 2011;4:104–7.
- 45. Angelberger S, Reinisch W, Messerschmidt A, Miehsler W, Novacek G, Vogelsang H, et al. Long-term follow-up of babies exposed to azathioprine in utero and via breastfeeding. J Crohns Colitis. 2011;5:95–100.
- Bernard N, Gouraud A, Paret N, Cottin J, Descotes J, Vial T. Azathioprine and breastfeeding: long-term follow-up. Fundam Clin Pharmacol. 2013;27(Suppl. 1):12.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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