Wish for child / pregnancy: How should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?

This chapter is based on the corresponding chapter in the previous versions of the guideline [1-3]. A new search was conducted, details of which can be found in the individual chapter, see below.

Indication for systemic therapy during pregnancy:

Psoriasis commonly affects men and women planning conception and women who are pregnant, so understanding the risks of therapy during conception and pregnancy is crucial. Psoriasis is not known to have a significant impact on either male or female fertility. Although pregnancy has an unpredictable effect on psoriasis, limited evidence suggests that psoriasis usually improves; around 55% improve during pregnancy, 25% report no change, and 25% worsen [4,5]. Conversely, in the post-partum period, psoriasis is more likely to flare; around 65% worsen, 25% demonstrate no change and 10% improve. Maternal and fetal health outcomes are vital considerations when deciding on the optimal treatment for individuals with psoriasis who are planning conception or are pregnant. Although data are limited and not always consistent across studies [6], untreated severe psoriasis in the mother may be detrimental for maternal outcomes, for example it has been shown to be associated with preterm birth, caesarean delivery and pre-eclampsia [7]. This (uncertain) risk of untreated psoriasis of the mother in pregnancy must therefore be weighed against any potential harm through drug exposure of the fetus. Other factors that may impact pregnancy outcomes include alcohol consumption, smoking and comorbidities such as obesity and depression (which are more prevalent in greater disease severity) [8]. Despite the rapidly increasing number of medications available for the treatment of psoriasis, knowledge on their safety in pregnancy remains limited, as outlined in this chapter.

As standard good practice, we suggest that family planning and contraception should be discussed with all patients of reproductive age when starting systemic agents. The decision to pause or continue medications during conception, pregnancy and breastfeeding is complex.[9] Careful discussion and counselling between clinician and patient are essential. The decision to pause or continue treatment will depend on several factors including the systemic agent being used, the degree of control of psoriasis achieved, the degree of difficulty in achieving disease control, concomitant psoriatic arthritis and disease severity during previous pregnancies, if relevant.

We **recommend** weighing the importance of sustaining disease control during pregnancy for maternal outcomes against any potential harm through drug exposure of the fetus.	↑↑	STRONG CONSENSUS 100 % Agreement Expert Consensus

Non-biologic systemic drugs

Acitretin

Acitretin is teratogenic and is contraindicated in women of child-bearing potential, those planning pregnancy, breastfeeding or not capable of using contraception until three years after cessation of therapy [10].

Apremilast

There are limited data about the use of the small molecule apremilast during pregnancy. Previous studies on animals did not show an increase in malformations with apremilast, but have shown dose-related fetal loss and reduced birth weight. Apremilast is therefore contraindicated during pregnancy [11]. Women of child-bearing potential should use effective contraception to prevent pregnancy and continue this until at least four weeks after cessation of apremilast treatment [11].

Apremilast was detected in the milk of lactating mice at levels approximately 1.5-fold that of blood plasma samples [12,13]. It is unknown whether apremilast or its metabolites are excreted in breast milk in humans, therefore apremilast should not be used whilst breastfeeding [11,13]. No data are available regarding the influence of apremilast on fertility in humans [11].

Ciclosporin

Ciclosporin crosses the placenta, but there is no evidence for teratogenicity [14]. Experience with solid organ transplant recipients indicates that ciclosporin increases the chance of pregnancy-specific complications such as pre-eclampsia and low birthweight. In pregnant women with plaque psoriasis receiving ciclosporin, the advantages and disadvantages of continuing ciclosporin should be considered. Ciclosporin should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus [14]. The ethanol content of the Sandimmun Neoral formulations should also be taken into account in pregnant women.

If necessary, ciclosporin treatment can be continued with close follow-up, preferably together with an obstetrician [14,15]. Ciclosporin is transferred into breast milk, therefore ciclosporin use is contraindicated during breastfeeding. There is limited data on the effect of ciclosporin on human fertility.

Dimethyl fumarate

Dimethyl fumarate is contra-indicated in women of child-bearing potential who are not using appropriate contraception [16]. Dimethyl fumarate should not be taken by women who are pregnant, breast-feeding or attempting conception. A systematic review evaluating pregnancy and fetal outcomes in multiple sclerosis did (among others) include women exposed to dimethyl fumarate in the first trimester but did not report outcomes by drug [17]. No data are available on the effects of dimethyl fumarate on human fertility [16]. In patients with diarrhea during treatment with dimethyl fumarate, the effect of oral contraceptives can be reduced. Additional use of barrier methods of contraception is therefore recommended [16].

It is unknown whether fumarates or their metabolites are excreted in breast milk, therefore the use of fumarates is contraindicated during breastfeeding [16].

Methotrexate

Methotrexate is a folic acid antagonist known to be teratogenic in humans. In a prior review, statistically significant higher proportions of microcephaly, craniosynostosis, tetralogy of Fallot, pulmonary valve atresia, limb reduction defects and syndactyly were found in newborns after maternal use of methotrexate in pregnancy [18]. Spontaneous abortions were observed more frequently in pregnant women receiving methotrexate (less than 30 mg/week) compared to women with comparable diseases treated with other medications (42.5% versus 22.5%) [19].

Therefore, where relevant, women should be counselled about pregnancy and breastfeeding, and should not conceive whilst taking methotrexate [19]. EMA guidelines recommend discontinuing methotrexate for 6 months before attempting conception, which is a change from the previous recommendations of 3 months [20]. No evidence pertaining to the standard dose of methotrexate (5-30mg/week) for inflammatory diseases is cited for this change of recommendation. The practice of the guideline group differs from this in favor of a shorter period of discontinuation (3 months).

It is recommended that sexually active women have a pregnancy test prior to starting therapy and use two methods of contraception throughout the period of methotrexate treatment. In the event of pregnancy during methotrexate therapy, immediate referral to an obstetrician is required [21]. Methotrexate influences oogenesis and possibly can reduce fertility, especially in high doses. In most patients this is reversible after stopping methotrexate [19]. Methotrexate is excreted into breast milk and so should not be used when breastfeeding.

Deucravacitinib

There are limited data about the use of the TYK2 inhibitor, deucravacitinib, during pregnancy. In animal studies, there was no observed effect on fertility or early embryonic development. Due to limited data, the license recommends avoiding deucravacitinib during pregnancy [22].

Recommendations (non-biologic systemic drugs):

When providing advice on use of systemic therapies in women planning conception or who are pregnant, prescribers are advised to use these recommendations with reference to the individual drug SmPC.

We **suggest** ciclosporin as a first line conventional agent in women planning conception and when it is necessary to start systemic therapy during the 2nd and 3rd trimester of pregnancy.	↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*
Methotrexate and acitretin are contra-indicated in women planning conception. We **recommend against** using these.	↓↓	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*
Fumarates, apremilast and deucravacitinib are contra-indicated in women planning conception. We **suggest against** using these.	↓	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS

* due to personal-financial conflict of interest 3 abstentions

Biologic drugs

Data from studies reporting pregnancy outcomes in women exposed to biologic treatments during conception and/or pregnancy were comprehensively reviewed as part of the British Association of Dermatologists guidelines for biologics use in psoriasis [23]. All of the biologic agents that are currently licensed for psoriasis except certolizumab pegol contain a human IgG1 Fc region and are actively transported across the placenta via neonatal Fc receptors [24,25]. Active placental transfer is thought to be very low during the first trimester when organogenesis takes place, hence the theoretical risk of teratogenicity of biologics is low. Active transfer can, however, occur at around 13 weeks' gestation and increases significantly after 20 weeks' gestation. This increasing exposure to biologics during the second and third trimesters is hypothesised to adversely affect fetal development, leading to potential risk of neonatal immunosuppression and greater risk of neonatal infections [26]. Biologic therapies typically disappear from an infant´s serum within the first six months of life although infliximab has been detected in the serum of infants exposed in utero up to the first 12 months of life [27].

In contrast, certolizumab pegol is the only PEGylated humanised antigen-binding fragment of a TNFi and it lacks a Fc domain [28]. Certolizumab pegol therefore does not bind to the human neonatal Fc receptor and it is not actively transferred across the placenta. This was underscored by an analysis of 31 pregnancies exposed to infliximab, adalimumab and certolizumab pegol (for inflammatory bowel disease), in which the median levels of infliximab, adalimumab and certolizumab pegol in the cord blood of infants compared with that of mother were 160%, 153%, and 3.9%, respectively [29]. Post-marketing prospective pharmacokinetic research has confirmed no/minimal transfer of certolizumab pegol via the placenta (CRIB study, n=16 [30]) and into breast milk (CRADLE study, n=19 [31]). A prospective study investigating breast milk transfer of biologics in women with inflammatory bowel disease found no/minimal levels of infliximab (29 women), adalimumab (21 women), certolizumab (13 women) or ustekinumab (6 women) detected in the breast milk of lactating women and there was no increase in infection rates in breastfed infants [32].

The majority of studies that report pregnancy outcomes in women exposed to biologics during conception and/or pregnancy are limited to TNFi exposure [33-45]. Evidence on the use of other biologics in pregnancy is limited. A systematic review identified 54 pregnancies with maternal exposure to ustekinumab (from cohort studies, registry data and case reports) and 5 pregnancies with maternal exposure to secukinumab (case reports) [46]. Further information from the Novartis safety database included 119 pregnancies with maternal exposure to secukinumab with most women discontinuing treatment in the first trimester [47]. Post-hoc analysis of phase I to III tildrakizumab clinical trials reported

14 pregnancies as protocol violations [48]. Tildrakizumab was discontinued after confirmation of pregnancy [48].

The available studies identified no clear evidence of drug-specific harm to the fetus following biologic exposure with respect to congenital malformations, live births, pre-term births or neonatal infections but data are limited, and drug exposure was generally limited to the first trimester [33-48]. Two studies (in inflammatory bowel disease) addressed maternal infection, indicating a potential increased risk to the mother following TNFi exposure [37,49].

The evidence is overall limited since most studies involved small cohorts that may be underpowered to demonstrate small but significant risks associated with the treatments. Most of the evidence also relates to women with other chronic inflammatory conditions such as inflammatory bowel disease or arthritis rather than psoriasis specifically. Several of the outcomes were poorly defined and heterogeneous, making it difficult to ascertain whether or not a pattern of specific birth defects was occurring. There is also a paucity of information on long-term outcomes for children born to women receiving biologics.

Recommendations (biologic drugs):

When providing advice on use of systemic therapies in women planning conception or who are pregnant, prescribers are advised to use these recommendations with reference to the individual drug SmPC.

All biologic drugs currently licensed for psoriasis (with the exception of certolizumab pegol) are actively transferred to the fetus during the second and third trimester, and the impact of this on neonatal development and risk of infection (to both mother and baby) has not been adequately studied.

We **recommend** certolizumab pegol as a first line choice when starting biologic therapy in women planning conception (when a biologic is considered essential to use in pregnancy) and when it is necessary to start a systemic therapy during the second or third trimester.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*
We **suggest** stopping biologic therapy in the second and third trimester (except certolizumab pegol) to minimise fetal exposure and limit potential infection risk to the neonate.	↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*

We **recommend against** using live or live attenuated vaccines in infants whose mothers received biologic therapy beyond 16 weeks gestation, unless the benefit of the vaccination clearly outweighs the theoretical risk of administration. (Refers to infants up to 6 months of age, or 12 months if there is maternal exposure to infliximab.)	↓↓	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS

* due to personal-financial conflict of interest 3 abstentions

Necessity for continuing contraception immediately following biologic treatment cessation

There is no consensus on how long contraception needs to be continued after stopping treatment with a biologic. For treatments with a good safety profile during pregnancy, continuation of contraception immediately following treatment cessation may not be as relevant as for treatments with an unknown or less favourable safety profile.

Conception and relevant information on biologic pharmacology

Active placental transfer of biologics starts to occur around 13 weeks' gestation and increases significantly after 20 weeks' gestation. Please refer to the relevant SmPC for drug-specific half-lives to determine timelines to drug clearance on stopping therapy, when / if this is planned (pre-conception, during pregnancy).

Paternal use

In men who are planning conception, the effects of systemic medications on both fertility and fetal development are important considerations. However, there are very limited data on the impact of paternal exposure to systemic medications, particularly with respect to teratogenicity and longer-term sequelae.

Acitretin

Acitretin has no known effect on male fertility [50]. Traces of acitretin have been reported in the semen of men, however there is no evidence of teratogenicity at conception as the main at risk period is 4–6 weeks later [51]. Although ongoing exposure via direct contact with semen during unprotected sexual

intercourse after conception is of low risk, the barrier method of contraception post-conception may be considered [12].

Apremilast

There are no available data for the impact of paternal exposure to apremilast on male fertility or pregnancy outcomes. In animal studies in mice, no adverse effects on fertility were observed in males at exposure levels threefold clinical exposure [2].

Ciclosporin

There is no evidence that paternal use of ciclosporin affects male fertility, however there are a paucity of studies on this [12,52,53]. Prior systematic reviews of cohort study data showed no impact on pregnancy outcomes [12,52]. This includes data from a Danish registry study of 247 children conceived during paternal use of ciclosporin, which found no association between paternal exposure to ciclosporin and increased risk of congenital abnormalities [54].

Fumarates

A European consensus meeting concluded that contraception for males receiving fumarates is not required, although there is a paucity of evidence [55].

Methotrexate

Fertility

A systematic review identified 48 male exposures to methotrexate [52], of which there were two isolated case reports of oligospermia (one reversible and one irreversible) [56,57]. Another five publications comprising the remaining 46 exposures concluded that there was no impact of methotrexate on male fertility [52]. A case series of 26 men receiving methotrexate who had their semen examined using radioactive phosphorus for testicular histology and spermatogenic function showed no negative impact on fertility [58]. Another study compared semen parameters from ten men treated with methotrexate for severe psoriasis with those of ten men using topical steroids, and found that those taking methotrexate were significantly more likely to have normal semen parameters [59].

Pregnancy outcomes

Paternal methotrexate use has not been shown to cause teratogenicity or adverse pregnancy outcomes. A systematic review which reported 1511 peri-conception paternal methotrexate exposures concluded that there was no link between paternal methotrexate exposure and adverse pregnancy outcomes or congenital malformations [52]. The largest cohort studies, comprising national registry data [54,60,61] and longer-term outcomes [62], showed no increased risk of paternal methotrexate exposure on pregnancy outcomes.

The above data are reassuring. However, a recent comprehensive review by the EMA concluded the need for ongoing caution on use of methotrexate during male conception [20]. EMA guidelines therefore recommend discontinuing methotrexate for three months before attempting conception [20]. This is a return to previous recommendations after the 2016 update had recommended a six-month washout period. No evidence pertaining to the standard dose of methotrexate (5-30mg/week) for inflammatory diseases is cited for these changes of recommendation. On discussion, it was noted that the practice of the guideline group varies in regard to the need for a washout period for methotrexate with some following EMA guidelines and others continuing methotrexate due to the lack of evidence of harm.

Biologics

Although there are limited available data, cohort studies of TNFi found no evidence for impairment in fertility during paternal use [12,53]. A systematic review highlighted that sperm motility and vitality may even improve under TNFi therapy, possibly due to a decrease in disease activity [63]. Cohort studies (total of 60 exposures with outcome events documented in 28 cases) involving a range of TNFi (adalimumab, certolizumab pegol, etanercept, infliximab) also demonstrated no evidence for an association between impaired pregnancy outcomes and paternal use of TNFi therapy at the time of conception [12,52,63].

There are scant data available assessing the potential impact of paternal exposure to other biologic agents including IL-12/IL-23p40 inhibitors, IL-17 inhibitors or IL-23p19 inhibitors on male fertility or pregnancy outcomes. A retrospective analysis of a de-identified medical and pharmacy administrative claims database (OptumLabs® Data Warehouse) showed no association between paternal ustekinumab exposure and increased risk of major congenital malformations, preterm birth or low birth weight. [64] The limited data available regarding paternal exposure to the IL-17 inhibitor secukinumab (from Novartis global safety database) suggested no clear evidence of drug specific harm following paternal biologic exposure with respect to risk of miscarriage or congenital malformations. [47]

For male patients, be aware that EMA guidance recommends discontinuing methotrexate for three months before attempting conception.	**Statement**	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS*
As a precaution, it is **suggested** that men taking acitretin use barrier forms of contraception post-conception to limit exposure via direct contact with semen during pregnancy.	↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS**

We **recommend** the collection of paternal exposure to medications during conception and pregnancy outcome data in national safety registries where available.	↑↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS**
We **suggest** that men may continue biologic therapy when planning conception.	↑	STRONG CONSENSUS 100 % Agreement EXPERT CONSENSUS**

* due to personal-financial conflict of interest 4 abstentions; ** due to personal-financial conflict of interest 3 abstentions

Review of the evidence on psoriasis and wish for child /pregnancy

Research question

How should psoriasis patients with a wish for pregnancy in the near future or who are pregnant be managed?

Screening criteria

	Inclusion criteria	Exclusion criteria
Patients	1. Adult patients with psoriasis or psoriasis arthritis with wish for child (maternal, paternal) or who are pregnant 2. Adult patients, regardless of the type of autoimmune disease, who are receiving the treatments listed below with wish for child (maternal, paternal) or who are pregnant	
Intervention	**Maternal population - conventional systemic treatment:** ciclosporin, fumarates **paternal population - conventional systemic treatment:** ciclosporin, fumarates, acitretin, MTX **both populations - biologicals:** TNFi: adalimumab, etanercept, certolizumab pegol, infliximab anti-IL12/23: ustekinumab anti-IL17: bimekizumab, brodalumab, ixekizumab, secukinumab anti-IL23: guselkumab, risankizumab, tildrakizumab **both populations – small molecules:** PDE4i: Apremilast tyrosine kinase 2 (TYK2) inhibitor: deucravacitinib (new, no filter for publication date applied))	**maternal population:** MTX and retinoids (rationale: No need to investigate further as contraindications are clear)
Comparator (if possible)	another included drug and/or placebo	
Outcomes	Maternal and fetal health outcomes Male and female fertility	
Study Design	Systematic reviews on human studies	Systematic reviews on animal studies non-systematic reviews primary studies in-vitro studies expert opinions without primary data

Information source and screening process

We conducted a search to identify new systematic reviews that have become available since the last guideline [3] was published. We searched MEDLINE via Ovid.

The search strategy included text words and MeSH terms for: pregnancy, fertility, maternal and paternal care, psoriasis, systemic treatments and use of biologics. We restricted the search to the article types 'systematic review' and 'meta-analysis' and to publication dates from September 2019 onwards, as shown below.

One methodologist conducted a topic-specific but non-systematic screening. The chapter authors then screened the included full texts based on the eligibility criteria, listed above.

Search strategy (May 04, 2023)

Filter for identification of systematic reviews and meta-analysis: *adapted* according to Wong et al., 2006 (high specificity) (https://pubmed.ncbi.nlm.nih.gov/17082841/)

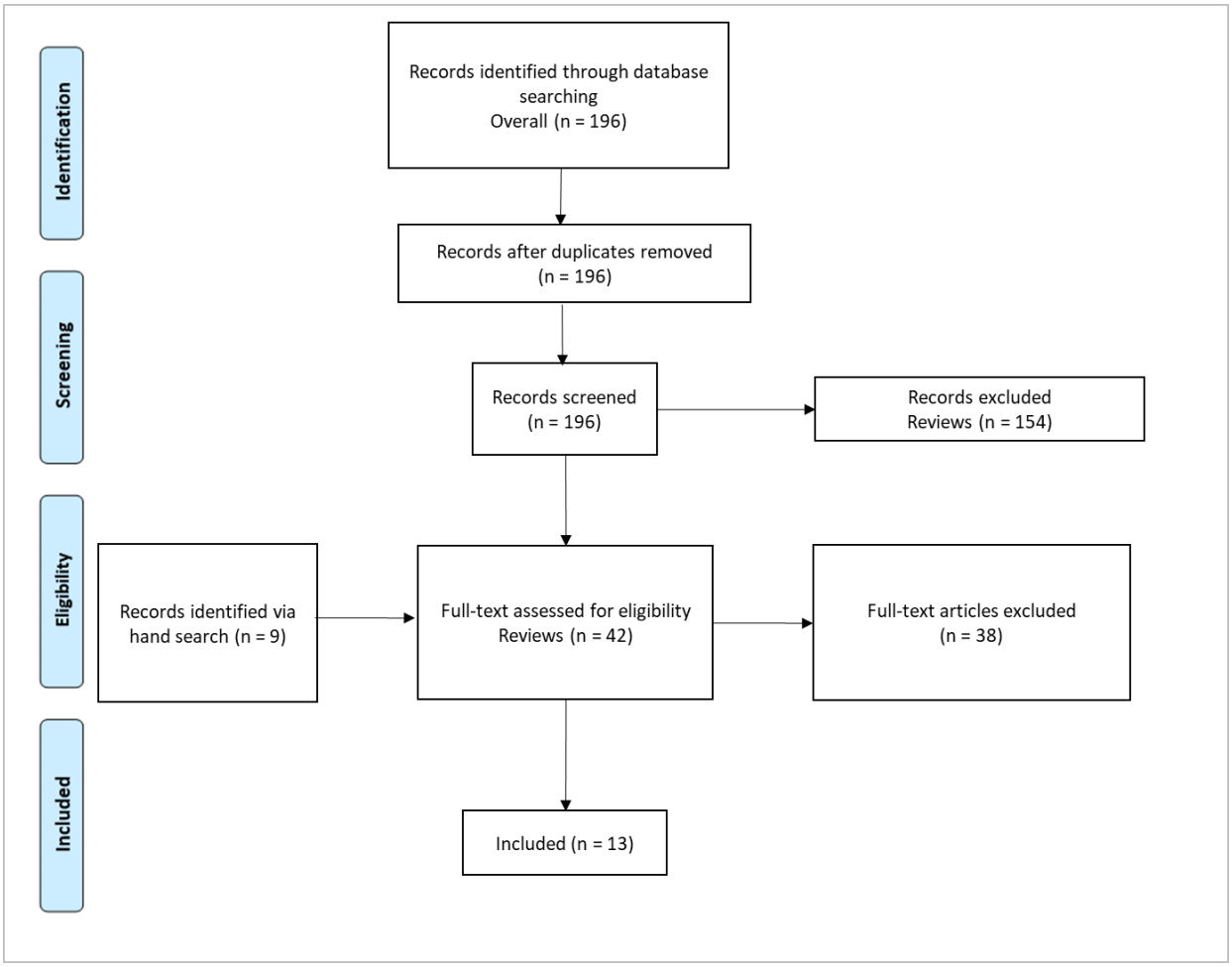
Ovid MEDLINE(R) ALL <1946 to May 04, 2023>

No.	Search term	Results	Comment
1	exp Methotrexate/	41173	Relevant for paternal population
2	methotrexate$.mp.	60167	
3	amethopterin.mp.	401	
4	mtx.ti,ab.	14821	
5	exp Fumarates/	5371	Relevant for maternal and paternal population
6	(fumar$ and esters).mp.	477	
7	dimethylfumarate.mp.	209	
8	fae.ti,ab.	1035	
9	dmf.ti,ab.	9886	
10	fumarate$1.mp.	21083	
11	Acitretin/	1301	Relevant for paternal population
12	((oral or orally or systemic) and retinoid$).ti,ab.	2962	
13	acitretin.mp.	2052	
14	Retinoids/	6346	
15	Ustekinumab.mp.	3091	Relevant for maternal and paternal population
16	secukinumab.mp.	1918	
17	apremilast.mp.	1057	
18	guselkumab.mp.	567	
19	exp antibodies, monoclonal/	274579	
20	monoclonal antibod$.mp.	206097	
21	exp Interleukin-23/ or exp Interleukin-12/ or Interleukin-17/	30452	
22	exp Interleukin-12 Subunit p40/ or p40 subunit.mp.	1906	
23	exp Tumor Necrosis Factors/ or exp Tumor Necrosis Factor-alpha/ or exp Receptors, Tumor Necrosis Factor, Type II/ or exp Receptors, Tumor Necrosis Factor/ or exp Receptors, Tumor Necrosis Factor, Type I/ or exp TNF-Related Apoptosis-Inducing Ligand/	197732	
24	(anti tumour necrosis factor or anti tumor necrosis factor).mp.	6277	
25	(tumor necrosis factor-alpha or tumour necrosis factor-alpha).mp.	191232	
26	anti tnf.mp.	12600	
27	(tnf antibod$ or tnf alpha antibod$).mp.	2392	
28	(tumour necrosis factor antibod$ or tumor necrosis factor antibod$).mp.	161	
29	(antitumor necrosis factor or antitumour necrosis factor).mp.	934	
30	exp Immunoglobulin Fab Fragments/	29525	
31	(infliximab$ or monoclonal antibody cA2).mp.	17477	
32	etanercept$.mp.	9656	
33	adalimumab$.mp.	10788	

No.	Search term	Results	Comment
34	Cyclosporine/	30551	
35	(Ciclosporin* or cyclosporin*).mp.	61903	
36	brodalumab.mp.	521	
37	ixekizumab.mp.	981	
38	certolizumab.mp.	1565	
39	Certolizumab Pegol/	728	
40	tildrakizumab.mp.	253	
41	bimekizumab.mp.	116	
42	risankizumab.mp.	370	
43	**or/5-10,15-42**	**723456**	
44	deucravacitinib.mp.	60	Relevant for maternal and paternal population
45	TYK2 Kinase/	626	
46	(TYK2 or tyrosine kinase 2).ti,ab.	2182	
47	**or/44-46**	**2308**	
48	psoria$.ti,ab.	58266	
49	exp Psoriasis/	47550	
50	palmoplantar$ pustulosis.ti,ab.	683	
51	pustulosis palmaris et plantaris.ti,ab.	173	
52	(pustulosis and palms and soles).ti,ab.	113	
53	**or/48-52**	**65051**	
54	(pregnan* or gravid* or gestation* or maternal* or mother* or pre-concept* or preconcept* or periconcept* or peri-concept* or antepart* or ante-part* or prepart* or pre-part* or antenatal* or ante-natal* or prenatal* or pre-natal* or inutero or in-utero or intrauterin* or intra-uterin* or f?etal* or f?eto* or f?etus* or embryo* or fertil* or infertil*).ti,ab,kf.	1717938	
55	Pregnant Women/	14127	
56	exp Pregnancy/	1000354	
57	exp Pregnancy Trimesters/	44646	
58	exp Pregnancy Complications/	472218	
59	Maternal Exposure/	11053	
60	Maternal Health/	2271	
61	Preconception Injuries/	54	
62	exp Prenatal Injuries/	34340	
63	Embryo, Mammalian/	51569	
64	exp "Embryonic and Fetal Development"/	309780	
65	exp Fetus/	166832	
66	Infertility, Female/	30893	
67	exp Fertility/	45938	
68	exp Fertilization/	25118	
69	**or/54-68**	**2239569**	

No.	Search term	Results	Comment
70	Paternal Exposure/	1194	
71	exp Infertility, Male/	31020	
72	exp Spermatozoa/	73332	
73	exp Semen Analysis/	29099	
74	exp Spermatogenesis/	22072	
75	exp Fathers/	10876	
76	exp Fertility/	45938	
77	exp Fertilization/	25118	
78	(sperm* or semen* or father* or paternal* or paternit* or fertil* or infertil*).ti,ab,kf.	441343	
79	or/70-78	473675	
80	cochrane database of systematic reviews.jn. or search:.tw. or meta analysis.mp,pt. or MEDLINE.tw. or systematic review.tw.	823840	Adapted filter for systematic reviews and meta-analyses
81	("201909*" or "201910*" or "201911*" or "201912*" or "2020*" or "2021*" or "2022*" or "2023*").dt.	5585359	Time filter
82	exp animals/ not humans.sh.	5118239	Filter to exclude animal studies
83	43 or 53	773337	
84	69 and 83	40637	
85	81 and 84	4508	
86	47 and 69	114	
87	85 or 86	4620	**Maternal population**
88	or/1-42,53	829616	
89	79 and 88	6616	
90	81 and 89	869	
91	47 and 79	19	
92	90 or 91	888	**Paternal population**
93	87 or 92	5003	Both populations
94	93 not 82	3742	Both populations without animal studies
95	**94 and 80**	**196**	**Final result: Aggregated evidence on both populations**

Flow chart



Full text screening and quality appraisal

Explanations

One methodologist assessed the methodological quality of the systematic reviews (SRs) using the AMSTAR-2 tool [65]. It can be rated as high, moderate, low and critically low.

The tool [65] contains 16 items, 7 of which are predefined as critical. If 1 of these critical items is not fulfilled, the quality of the SR can only be rated as low. If ≥ 2 critical items are not fulfilled, the SR is rated as critically low.

Table 1: AMSTAR-2 results

Quality	**High**	**Moderate**	**Low**	**Critically low**	**Retracted/ off topic/ additional value unclear**
Number (n/N)	1/42	0	5/42	33/42	3/42

3 of the low rated SRs were conducted for paternal population, one in mothers with PsA and one in mothers with atopic diseases, treated with Omalizumab and Rituximab.

In case the information from low quality SRs is not sufficient to process the chapter and a critically low SR has to be included, we have attempted to distinguish by the number of critical items not met and to identify critically low SRs whose methodological quality appears to be just acceptable:

Table 2: Quality categories

Category	Explanation	Frequency
1	low quality or better	6
2	Critically low quality with 2 critical items not fulfilled	4
3	Critically low quality with > 2 critical items not fulfilled	23
4	Critically low quality and Item 4 (comprehensive search) not fulfilled	6

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