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 previous chapter [1,2]. A systematic search was conducted, details of which can be found in the Methods & Evidence Report**.**

Results/Answer:

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 [3,4]. 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 [5], untreated severe psoriasis in the mother may be detrimental for fetal well-being and pregnancy outcomes, for example it has been shown to be associated with preterm birth and low birthweight babies [6,7]. The 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.

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 [9].

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

[10]. 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 [10].

Apremilast was detected in the milk of lactating mice at levels approximately 1.5-fold that of blood plasma samples [11,12]. It is unknown whether apremilast or its metabolites are excreted in breast milk in humans, therefore apremilast should not be used whilst breastfeeding [10,12]. No data are available regarding the influence of apremilast on fertility in humans [10].

Ciclosporin

Ciclosporin crosses the placenta, but there is no evidence for teratogenicity [13]. 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 [13]. 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 [13,14]. 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 [15]. Dimethyl fumarate should not be taken by women who are pregnant, breast-feeding or attempting conception. There are no published reports of patients becoming pregnant while on dimethyl fumarate [16]. No data are available on the effects of dimethyl fumarate on female fertility [15]. 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 [15].

It is unknown whether fumarates or their metabolites are excreted in breast milk, therefore the use of fumarates is contraindicated during breastfeeding [15].

Methotrexate

Methotrexate is a folic acid antagonist known to be teratogenic in humans. In a recent 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 [17]. 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%) [18].

Therefore, where relevant, women should be counselled about pregnancy and breastfeeding, and should not conceive whilst taking methotrexate [18]. Recent EMA guidelines recommend discontinuing methotrexate for 6 months before attempting conception, which is a change from the previous recommendations of 3 months [19]. 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 [20]. Methotrexate influences oogenesis and possibly can reduce fertility, especially in high doses. In most patients this is reversible after stopping methotrexate [18]. Methotrexate is excreted into breast milk and so should not be used when breastfeeding.

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 convention agent in women planning conception and when it is necessary to start systemic therapy during the 2nd and 3rd trimester of pregnancy	↑	STRONG CONSENSUS[1]  EXPERT CONSENSUS
Methotrexate and acitretin are contra-indicated in women planning conception. We **recommend against** using these.	↓↓	
Fumarates and apremilast are contra-indicated in women planning conception. We **suggest against** using these.	↓	
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems	↑↑	
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available.	↑↑	

[1] 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 recently comprehensively reviewed as part of the British Association of Dermatologists guidelines for biologics use in psoriasis [21]. 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 [22,23]. 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 [24]. Biologic therapies typically disappear from an infant´s serum within the first six months of life.

In contrast, certolizumab pegol is the only PEGylated humanised antigen-binding fragment of a TNF antagonist and it lacks a Fc domain [25]. 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 [26]. Infliximab and adalimumab could be detected in the infants for as long as 6 months. Post-marketing prospective pharmacokinetic research has confirmed no/minimal transfer of certolizumab pegol via the placenta (CRIB study, n=16 [27]) and into breast milk (CRADLE study, n=19 [28]). Population-based cohort studies that report pregnancy outcomes in women exposed to biologics during conception and/or pregnancy are limited to TNF antagonist exposure only [29-41] (see respective table). No evidence was identified on the use of IL-12/IL-23p40, IL-17 or IL-23p19 inhibitor biologics. Overall, the available studies identified no clear evidence of drug-specific harm to the fetus following TNF antagonist exposure with respect to congenital malformations, live births, pre-term births or neonatal infections [29-41]. One study (in inflammatory bowel disease) addressed maternal infection, indicating a potential increased risk to the mother following TNF antagonist exposure [33].

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 **suggest** 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[1] 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.	↑	
We **suggest against** using live or live attenuated vaccines in infants (up to 6 months of age) whose mothers received biologic therapy beyond 16 weeks gestation, unless the benefit of the vaccination clearly outweighs the theoretical risk of administration.	↓	
We **recommend** consultation and information sharing across specialties, including with an obstetrician with expertise in caring for pregnant women with medical problems	↑↑	
We **recommend** the collection of maternal exposure to medications and pregnancy outcome data in national safety registries where available.	↑↑	

[1] 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. Table 47 gives an overview of the recommended minimum time lag between stopping a biologic treatment and conception, as stated in the respective SmPCs. 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. It is worth noting, that active placental transfer of biologics starts to occur around 13 weeks' gestation and increases significantly after 20 weeks' gestation. The specific half-lives of the respective drugs impact the remaining drug level at these time points.

Table 47: Overview of minimum time between stop of treatment and conception as given by respective SmPC

Infliximab	Adalimumab	Etanercept	Ustekinumab	Secukinumab	Apremilast*
6 months [133]	5 months [32]	3 weeks [382]	15 weeks [88]	20 weeks [80]	No information provided in SmPC, 28 days advised by Celgene

Ixekizumab	Certolizumab	Bimekizumab	Brodalumab	Tildrakizumab	Guselkumab	Risankizumab
10 weeks	5 months*	17 weeks	12 weeks	17 weeks	12 weeks	21 weeks

* Note: Certolizumab is the suggested biologic treatment option, for women who are planning conception or are pregnant and require a systemic therapy, see also respective chapters

Paternal use

In men who are planning conception, the effects of systemic medications on both fertility and fetal development are important considerations. However, there is 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 [42]. 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 [43]. 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 [11].

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 [11,44,45]. Recent systematic reviews of cohort study data showed no impact on pregnancy outcomes [11,44]. 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 [46].

Fumarates

A recent European consensus meeting concluded that contraception for males receiving fumarates is not required, although there is a paucity of evidence [15]

Methotrexate

Fertility

A recent systematic review identified 48 male exposures to methotrexate [44], of which there were two isolated case reports of oligospermia (one reversible and one irreversible) [47,48]. Another five publications comprising the remaining 46 exposures concluded that there was no impact of methotrexate on male fertility [44]. 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 [49]. 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 [50].

Pregnancy outcomes

Paternal methotrexate use has not been shown to cause teratogenicity or adverse pregnancy outcomes. A recent 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 [44]. The largest cohort studies, comprising national registry data [46,51,52] and longer term outcomes [53], showed no increased risk of paternal methotrexate exposure on pregnancy outcomes.

Although the above data do not support the need for any washout period for methotrexate, further evidence is required before this can be recommended. Recent EMA guidelines recommend discontinuing methotrexate for six months before attempting conception, which is a change from the previous recommendations of three months [19]. 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).

Biologics

Although there is limited available data, cohort studies of TNF antagonists found no evidence for impairment in fertility during paternal use [11,45]. A systematic review highlighted that sperm motility and vitality may even improve under TNF antagonist therapy, possibly due to a decrease in disease activity [54]. Cohort studies (total of 60 exposures with outcome events documented in 28 cases) involving a range of TNF antagonists (adalimumab, certolizumab pegol, etanercept, infliximab) also

demonstrated no evidence for an association between impaired pregnancy outcomes and paternal use of TNF antagonist therapy at the time of conception [11,44,54].

There are no studies which have assessed 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.

It is **recommended** that men discontinue methotrexate 3 months before attempting conception. * *EMA recommends 6 months as a means of precaution, the practice of the guideline group differs from this.	↑↑	STRONG CONSENSUS[1]  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.	↑	
We **recommend** the collection of paternal exposure to medications during conception and pregnancy outcome data in national safety registries where available.	↑↑	

[1] due to personal-financial conflict of interest 3 abstentions

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