Safety of Systemic Therapies for Psoriasis on Reproductive Potential and Outcomes

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Background

- The effects of systemic therapies for psoriasis on pregnancy outcomes, lactation and male fertility and mutagenicity are common concerns.
- We assessed the safety profile of commonly used conventional and biologic therapies for psoriasis in individuals of reproductive potential.

Methods

Literature searches were conducted through MEDLINE and The Cochrane Library. The summary of product characteristics (SPC) of the drugs were obtained via the electronic medicines compendium.

Results

Table 1 - Summary table of current evidence and guidelines on systemic psoriasis therapies and reproductive potential

Medication	FDA pregnancy category	Evidence	Embryo growth effects	Congenital malformation	Affected trimesters	Pregnancy Recommendations and Advice
Ciclosporin	C	Case and cohort studies	Premature birth and low birth weight	-	-	Consider in severe debilitating psoriasis (National Psoriasis Foundation)
Fumaric acid esters	C (dimethyl fumarate)	Animal models	Intrauterine growth retardation, lethality (animal models)	-	-	Contraindicated due to lack of evidence
Methotrexate	X	Case reports and cohort studies	Lethality	"Aminopterin syndrome" – CNS, skeletal, cardiac, pulmonary involvement	First trimester	Contraindicated in pregnancy, contraception for 3 months after cessation (BAD)
Acitretin	X	Case reports	Low birth weight	Craniofacial dysmorphias Hip malformations Meningo-myelocele Meningo-encephalocele, Multiple-synostosis Limb abnormalities	All trimesters	Contraindicated in pregnancy, contraception for 3 years before conception(BAD)
Infliximab	B	Case reports, clinical trials, adverse events database, Safety registry	Potential abortifacient Decreased postnatal immunity of newborn (infliximab)	Contentious links to VACTERL syndrome	End of second to third trimester	Consider as fourth line treatment after topicals, UVB phototherapy and ciclosporin. Advise a delayed immunisation schedule of live vaccines / BCG for the newborn Advise low risk in first trimester (infliximab and adalimumab)
Etanercept						
Adalimumab						
Ustekinumab		Case reports	-	-	-	Contraindicated due to lack of evidence

US FDA category

A – Reserved for substances shown, through controlled human studies, to have no fetal risk
B – Implies no evidence of fetal risk in humans based on animal studies
C – Includes drugs in which risk cannot be ruled out due to inadequate data
D – Includes drugs with positive evidence of fetal risk, may only be used in cases where the potential benefit outweighs the risk
X – Includes drugs that are absolutely contraindicated during pregnancy because proven fetal risks outweigh any potential benefits

Table 2 - Summary table of current evidence and guidelines on systemic psoriasis therapies and lactation

Medication	Evidence	Present in breast-milk?	Absorbed and present in infant serum?	Breast feeding recommendations in current guidelines
Ciclosporin	Case series	Yes	Yes(1 out of 5 infants)	Avoid in breast feeding (American Association of Paediatrics, National Psoriasis Foundation)
Fumaric acid esters	-	-	-	Contraindicated due to lack of evidence
Methotrexate	1 case report	Yes	-	Contraindicated due to lack of evidence (BSR/BAD)
Acitretin	1 case report	Yes	-	Contraindicated due to lack of evidence (BAD)
Infliximab	Case series	Yes	Yes (1 case)	Avoid breastfeeding, potential transfer to infant and therefore immunosuppression
Etanercept	Case reports	Yes	-	
Adalimumab	Case series	Yes	-	
Ustekinumab	Animal models	Yes (animal models)	-	Contraindicated due to lack of evidence

Table 3 - Summary table of current evidence and guidelines on systemic psoriasis therapies and male fertility and teratogenicity.

Medication	Evidence	Decreased fertility?	Congenital malformations	Paternal recommendations
Ciclosporin	Case series	Dose-related – may impair fertility at doses >4mg/kg/day	-	May decrease fertility, in particular at doses equivalent to or above 4mg/kg. Reassurance post-conception.
Fumaric acid esters	-	-	-	Contraindicated due to lack of evidence
Methotrexate	Case reports, Case series from registry	Dose related oligospermia and azoospermia	No evidence of increased incidence	Avoid conception for 3 months after cessation of methotrexate
Acitretin	Case series	-	1 case out of 25	No evidence of teratogenicity
Infliximab	Case series, safety data	Yes (1 case), unclear overall	1 case of hydrocephalia	No evidence of teratogenicity. May improve fertility. Reassurance in cases post-conception.
Etanercept		-	-	
Adalimumab		Yes (1 case), unclear overall	-	
Ustekinumab	Animal models	-	-	Contraindicated due to lack of evidence

Recommendations

- Ciclosporin should be considered as a third-line therapy after topical and UVB treatments for severe psoriasis in pregnancy.
- Anti-TNFs should be considered as a fourth-line therapy in pregnancy. They should be prescribed with consideration for suspension during late second trimester, with a delayed immunisation schedule for live virus vaccines and BCG if indicated.
- Breast-feeding should be avoided until further evidence becomes available in all systemic therapies.
- Fumaric acid esters, methotrexate and ustekinumab are not recommended in male patients intending to start a family until further evidence becomes available.