SCUOLA DERMATOLOGICA
SERGIO CHIMENTI
ROMA, 8-9 GIUGNO 2018
SUMMER MEETING

UNIVERSITÀ CATTOLICA del Sacro Cuore

Farmaci anti TNF-alpha e gravidanza

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Impatto della gravidanza sulla psoriasi

In gravidanza

la psoriasi a placche

- Migliora nel 55-56 %
- Rimane stabile nel 16-21%
- Peggiora nel 23-24% circa

l'artrite psoriasica

- Migliora nell'80%

L'aumento del rapporto estrogeni/progesterone correla con il miglioramento della psoriasi.

Dopo il parto

la psoriasi a placche

- Peggiora nel 50-65%
- Rimane invariata nel 20%
- Migliora in meno del 10%

l'artrite psoriasica

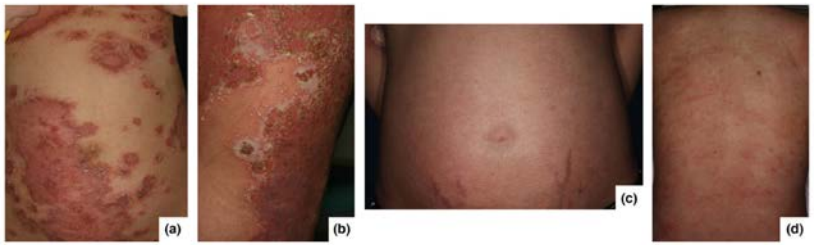
- Esordisce nel 30-40% dei casi
- Peggiora nel 70%

•*Farber , Nall, 1974; Dunna & Finlay, 1989; Ostensen, 1992; Boyd et al, 1996; Mowad et al, 1998;* Raychaudhuri et al 2003; *Murase et al, 2005*

Japanese Dermatological Association
THE JOURNAL OF DERMATOLOGY
doi: 10.1111/1346-8138.13429
Journal of Dermatology 2016; ●●: 1–2

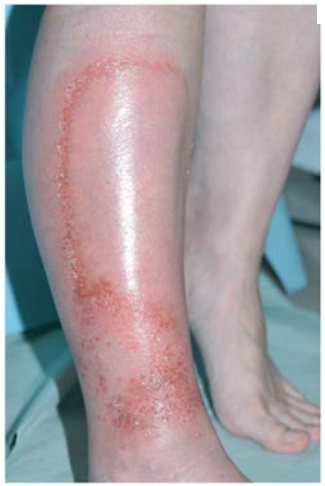
LETTER TO THE EDITOR

Case of generalized pustular psoriasis exacerbated during pregnancy, successfully treated with infliximab



Generalized pustular psoriasis of pregnancy treated with infliximab

N. Sheth, D. T. Greenblatt,* K. Acland,†
J. Barker and F. Teixeira‡



Clinical and Experimental Dermatology, **34**, 518–540

Dermatology

Dermatology 2010;220:71–76
DOI: 10.1159/000262284

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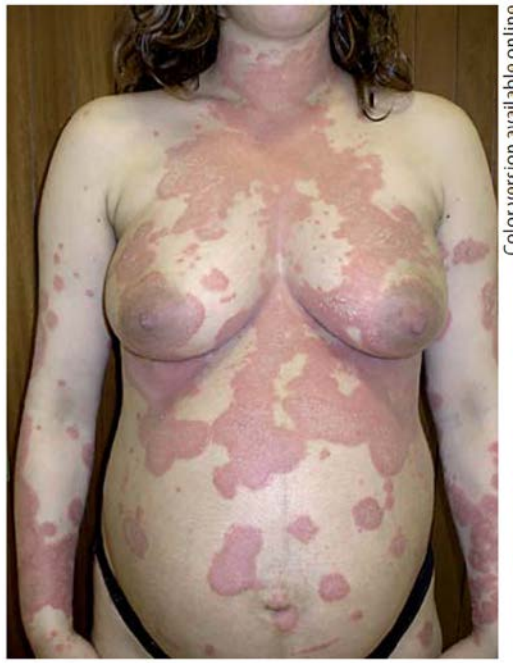
Treatment of Psoriasis with Anti-TNF Drugs during Pregnancy: Case Report and Review of the Literature

Lluís Puig Didac Barco Agustín Alomar



Color version available online

idence on successful infliximab treatment in pregnant women, with the first case of a patient with psoriasis who presented impetigo herpetiformis during her previous pregnancy. No detectable adverse effects were detected in the neonate, despite potential exposure to infliximab throughout gestation and breastfeeding. Even though absolute

Impatto della psoriasi sul decorso della gravidanza e sul suo esito

- Severità di malattia
- Comorbidità
- Stile di vita (es.fumo,consumo di alcolici,etc)
- Esposizione ai farmaci in corso di concepimento e nelle diverse fasi della gravidanza

Original Article | Journal of INTERNAL MEDICINE

Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study

2010 268;329–337

Results. Amongst 1199 women with RA, 7.8% gave birth between 32 and 36 gestational weeks (adjusted OR, 1.44; 95% CI, 1.14–1.82), 1.4% gave birth before gestational week 32 (adjusted OR, 1.55; 95% CI, 0.97–2.47), 1.6% had an infant with a low Apgar score (OR, 0.99; 95% CI, 0.95–1.65), 5.9% had an SGA birth (adjusted OR, 1.56; 95% CI, 1.2–2.01), 0.9% experienced stillbirth (adjusted OR, 2.07; 95% CI, 0.98–4.35) and 4.3% gave birth to an infant with congenital abnormalities (adjusted OR, 1.32; 95% CI, 0.98–1.79). The OR for congenital abnormalities decreased from 2.57 (95% CI, 1.59–4.16) in 1994–1997 to 1.00 (95% CI, 0.64–1.56) in 2002–2006.

Conclusions. Women with RA had a high prevalence of most adverse birth outcomes. This could be due to inflammatory activity, medical treatment or other factors not controlled for.

A meta-analysis on the influence of inflammatory bowel disease on pregnancy

J Cornish, E Tan, J Teare, T G Teoh, R Rai, S K Clark, P P Tekkis

Gut 2007;**56**:830–837. doi: 10.1136/gut.2006.108324

See end of article for authors' affiliations

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Revised 27 September 2006
Accepted
30 September 2006
Published Online First
21 December 2006

Background: Inflammatory bowel disease (IBD) has a typical onset during the peak reproductive years. Evidence of the risk of adverse pregnancy outcomes in IBD is important for the management of pregnancy to assist in its management.

Aim: To provide a clear assessment of risk of adverse outcomes during pregnancy in women with IBD.

Design: The Medline literature was searched to identify studies reporting outcomes of pregnancy in patients with IBD. Random-effect meta-analysis was used to compare outcomes between women with IBD and normal controls.

Patients and setting: A total of 3907 patients with IBD (Crohn's disease 1952 (63%), ulcerative colitis 1113 (36%)) and 320 531 controls were reported in 12 studies that satisfied the inclusion criteria.

Results: For women with IBD, there was a 1.87-fold increase in incidence of prematurity (<37 weeks gestation; 95% CI 1.52 to 2.31; p<0.001) compared with controls. The incidence of low birth weight (<2500 g) was over twice that of normal controls (95% CI 1.38 to 3.19; p<0.001). Women with IBD were 1.5 times more likely to undergo caesarean section (95% CI 1.26 to 1.79; p<0.001), and the risk of congenital abnormalities was found to be 2.37-fold increased (95% CI 1.47 to 3.82; p<0.001).

Conclusion: The study has shown a higher incidence of adverse pregnancy outcomes in patients with IBD. Further studies are required to clarify which women are at higher risk, as this was not determined in the present study. This has an effect on the management of patients with IBD during pregnancy, who should be treated as a potentially high-risk group.

SYSTEMATIC REVIEW

BJD
British Journal of Dermatology

Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies*

R. Bobotsis,[1] W.P. Gulliver,[2] K. Monaghan,[3] C. Lynde[4,5] and P. Fleming[5]

Br J Dermatol. 2016 Sep;175(3):464-72.

" We hypothesized that the immune dysregulation occurring in psoriasis, as in other autoimmune diseases, will negatively affect the normal progression of pregnancy and result in adverse pregnancy outcomes (*caesarean section, small for gestational age, low birth weight, very low birth weight, premature birth, congenital abnormalities, macrosomia, spontaneous abortion and stillbirth*)".

The primary objective of this systematic review was **to determine whether psoriasis has any effect on fetal morbidity and mortality** in adult women with psoriasis compared to women without psoriasis

The Impact of Psoriasis on Pregnancy Outcomes

Xinaida T. Lima[1,2], Vanitha Janakiraman[3], Michael D. Hughes[2] and Alexandra B. Kimball[1]

Psoriasis is an inflammatory disease that affects women in their reproductive years. Other similar diseases have been associated with adverse pregnancy outcomes. We sought to assess whether pregnant women with psoriasis are at higher risk of developing complications, such as preterm birth (PTB) and low birth weight (LBW). A retrospective cohort, performed at two large tertiary centers, evaluated the outcomes of 162 pregnancies in 122 women with psoriasis and 501 pregnancies in 290 women without psoriasis. Univariable and multivariable analyses, adjusting for important demographic factors, comorbidities, or a propensity score, were performed to evaluate the association of psoriasis and a poor outcome composite (POC), including PTB (<37 gestational weeks) and LBW (<2,500 g). Repeated measures analysis was used to account for the multiple pregnancies per woman. Cesarean delivery, preeclampsia/eclampsia, and spontaneous abortion were also evaluated. For women with psoriasis, there was a 1.89-fold increase in odds of POC (95% CI 1.06–3.39) in the univariable analysis. This effect remained statistically significant in the multivariable analyses. Psoriasis was not associated with cesarean delivery, preeclampsia/eclampsia, and spontaneous abortion. This study has shown higher odds of POC in patients with psoriasis. Further larger population-based studies are required to confirm these findings.

Journal of Investigative Dermatology (2012) **132**, 85–91; doi:10.1038/jid.2011.271; published online 15 September 2011

Psoriasis and pregnancy outcomes: A nationwide population-based study

Ya-Wen Yang, MD, MS,[a] Chin-Shyan Chen, PhD,[b] Yi-Hua Chen, PhD,[c] and Herng-Ching Lin, PhD[d]
Taipei, Taiwan

Background: Previous research regarding pregnancy outcomes in women with psoriasis either used selective hospital-based data, or analyzed obstetric, but not infant-specific, outcomes.

Objective: We sought to investigate whether maternal psoriasis was associated with increased risk of adverse pregnancy outcomes, compared with unaffected mothers, in an unselected nationwide population-based data set.

Methods: In total, 1463 mothers with psoriasis and 11,704 randomly selected mothers without psoriasis were included. Of the 1463 mothers with psoriasis, 645 (44.1%) who had received photochemotherapy or systemic therapy within 2 years before their index deliveries were put in the severe psoriasis group. Conditional logistic regression analyses were conducted to calculate the risk of low birth weight (LBW), preterm birth, cesarean section, small for gestational age, and preeclampsia or eclampsia for these two groups, after adjusting for characteristics of the mother, father, and infant.

Results: The odds of LBW for women with severe psoriasis were 1.40 times those of mothers without psoriasis (95% confidence interval = 1.04-1.89) after adjusting for characteristics of the mother, father, and infant. However, mothers with mild psoriasis had no significantly higher odds of LBW, preterm birth, cesarean section, infants small for gestational age, and preeclampsia or eclampsia compared with those without psoriasis.

Limitations: Patients with psoriasis were identified by diagnostic code in database, resulting in the possibility of misclassification bias. In addition, lack of information regarding maternal risk behaviors and previous adverse pregnancy outcomes may leave residual confounding.

Conclusion: We found that pregnant women with severe psoriasis had an increased risk of LBW infants, whereas mild psoriasis was not associated with excess risk of adverse birth outcomes. (J Am Acad Dermatol 2011;64:71-7.)

SYSTEMATIC REVIEW

BJD
British Journal of Dermatology

Psoriasis and adverse pregnancy outcomes: a systematic review of observational studies*

R. Bobotsis,[1] W.P. Gulliver,[2] K. Monaghan,[3] C. Lynde[4,5] and P. Fleming[5]

Br J Dermatol. 2016 Sep;175(3):464-72.

Limitations

" This systematic review attempted to answer a research question with **very limited published data** and therefore our sample size is relatively small and may be **underpowered to detect the uncommon pregnancy outcomes** we examined".

"There were a **wide variety of clinical settings** from which patients were studied, differences in the concomitant exposure to drugs and type of drug used around the time of pregnancy and variations in how or if the severity of psoriasis was defined, **all of which can have an impact on the outcome".**

Potentially modifiable risk factors for adverse pregnancy outcomes in women with psoriasis

G. Bandoli,* D.L. Johnson,* K.L. Jones,*† J. Lopez Jiminez,* E. Salas,* N. Mirrasoul,* A.S. Van Voorhees‡ and C.D. Chambers*†§

• British Journal of Dermatology 2010 **163,** pp334–339

Objectives To determine if pregnant women with psoriasis have an excess of potentially modifiable risk factors for adverse pregnancy outcomes.

Methods Prospectively collected data from the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project were analysed to compare the prevalence of selected risk factors between 170 pregnant women with psoriasis and 158 nondiseased controls.

Results Women with psoriasis were more likely to be overweight/obese prior to pregnancy ($P < 0{\cdot}0001$), to smoke ($P < 0{\cdot}0001$), or to have a diagnosis of depression ($P = 0{\cdot}03$), and were less likely to have been taking preconceptional vitamin supplements ($P = 0{\cdot}004$). After controlling for race/ethnicity and socioeconomic status, women with psoriasis were 2·37 (95% confidence interval 1·45–3·87) times more likely to be overweight/obese as women without psoriasis. Duration of disease, age at onset, measures of disease impact during pregnancy, or use of biologics in pregnancy were not significant predictors of overweight/obesity in the subset of psoriatic women.

Conclusions Pregnant women with psoriasis may be at increased risk for adverse pregnancy outcomes due to comorbidities or other health behaviours associated with the disease. These should be taken into consideration during clinical treatment of women with psoriasis who are in their childbearing years.

IMPIEGO E SAFETY DEI FARMACI PER LA PSORIASI IN GRAVIDANZA

Esistono pochi dati riguardanti l'uso di farmaci in gravidanza poiché questa categoria di pazienti viene di norma esclusa dagli studi clinici per motivi etici.

La maggior parte delle informazioni sugli effetti dei farmaci sul feto derivano dall'inavvertita esposizione della donna non ancora consapevole del suo stato di gravidanza o dal loro utilizzo in altra tipologia di pazienti.

Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments

US FDA pregnancy categories

Category	Description
A	Adequate and well-controlled human studies fail to show a fetal risk
B	Animal studies fail to show a fetal risk, and there are no human studies
C	Animal studies show a fetal risk, and there are no adequate human studies
D	There is evidence of fetal risk, but the benefits may outweigh the risk
X	There is evidence of fetal risk, and the risks clearly outweigh any possible benefits

N. Bangsgaard et a Am J Clin Dermatol 2015

- Classe A : nessun rischio emerso da studi controllati in donne in gravidanza

  Nessun farmaco

- Classe B : Non hanno mostrato effetti teratogeni, né tossicità negli animali. Non esistono studi controllati nell'uomo.

  - Farmaci biologici

    La scarsità dei dati disponibili sulla sicurezza di tali farmaci consigliano di interrompere il trattamento in gravidanza e nell'allattamento

- Classe C : l'uso è da riservarsi a quei casi in cui il beneficio giustifica il rischio potenziale

  - Calcipotriolo e altri derivati della vit. D3
  - Corticosteroidi topici e sistemici
  - Ciclosporina A
  - Ditranolo e derivati antrachinonici
  - PUVA-terapia
  - Tacrolimus

- Classe X : uso assolutamente controindicato in gravidanza
  - Acitretina
  - Methotrexate
  - Leflunomide
  - Tazarotene
  - Re-PUVA-terapia

- Classe A : nessun rischio emerso da studi controllati in donne in gravidanza

  Nessun farmaco

- Classe B : Non hanno mostrato effetti teratogeni, né tossicità negli animali. Non esistono studi controllati nell'uomo.

  - Farmaci biologici

    La scarsità dei dati disponibili sulla sicurezza di tali farmaci consigliano di interrompere il trattamento in gravidanza e nell'allattamento

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  - Leflunomide
  - Tazarotene
  - Re-PUVA-terapia

- Classe A : nessun rischio emerso da studi controllati in donne in gravidanza

  Nessun farmaco

- Classe B : Non hanno mostrato effetti teratogeni, né tossicità negli animali. Non esistono studi controllati nell'uomo.
  - Farmaci biologici

    La scarsità dei dati disponibili sulla sicurezza di tali farmaci consigliano di interrompere il trattamento in gravidanza e nell'allattamento

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  - Leflunomide
  - Tazarotene
  - Re-PUVA-terapia

Anti-TNF alpha e rischio teratogeno

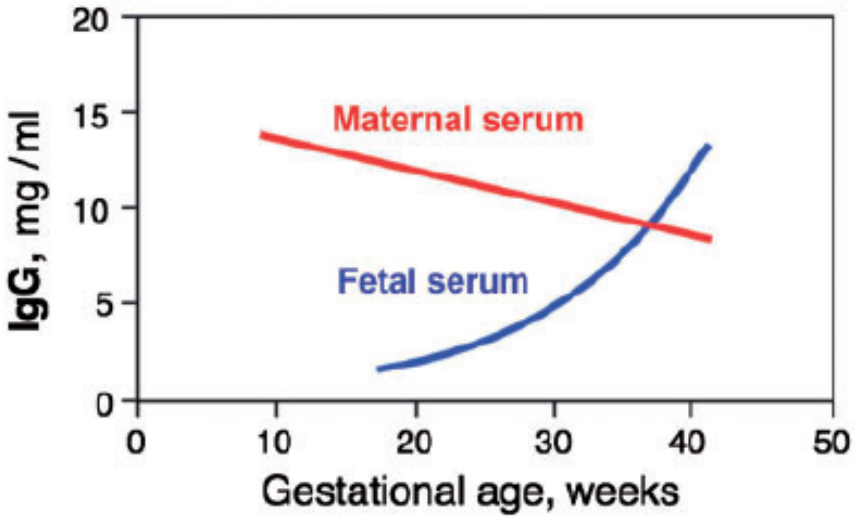
TNF-α inhibitor type	Type of studies	Number of human pregnancies exposed	Effect on pregnancy/child
Infliximab: complete IgG1 antibody	Case reports, cohort studies, case-control, registry data	>1000	No increase in miscarriage or malformations; no malformation pattern detected
Etanercept: fusion protein with Fc part	Case reports, cohort studies, case-control, registry data	>500	No increase in miscarriage or malformations; no malformation pattern detected
Adalimumab: complete IgG1 antibody	Case reports, cohort studies, case-control	>300	No increase in miscarriage or malformations; no malformation pattern detected
Golimumab: complete IgG1 antibody	Registry data	40	Data not conclusive
Certolizumab: pegylated Fab fragment	Registry data and case reports	139	No increase in miscarriage or malformations; no malformation pattern detected

Ostensen M. **Ann N Y Acad Sci** ***2014; 1317: 32–38***

Passaggio transplacentare delle IgG

Il livello di IgG nel sangue materno diminuisce durante la gravidanza in concomitanza con un aumento delle IgG di origine materna nel sangue fetale a partire dalla settimana 13 di gestazione

A fine gravidanza il livello di IgG nel sangue fetale è superiore rispetto a quello nel sangue materno

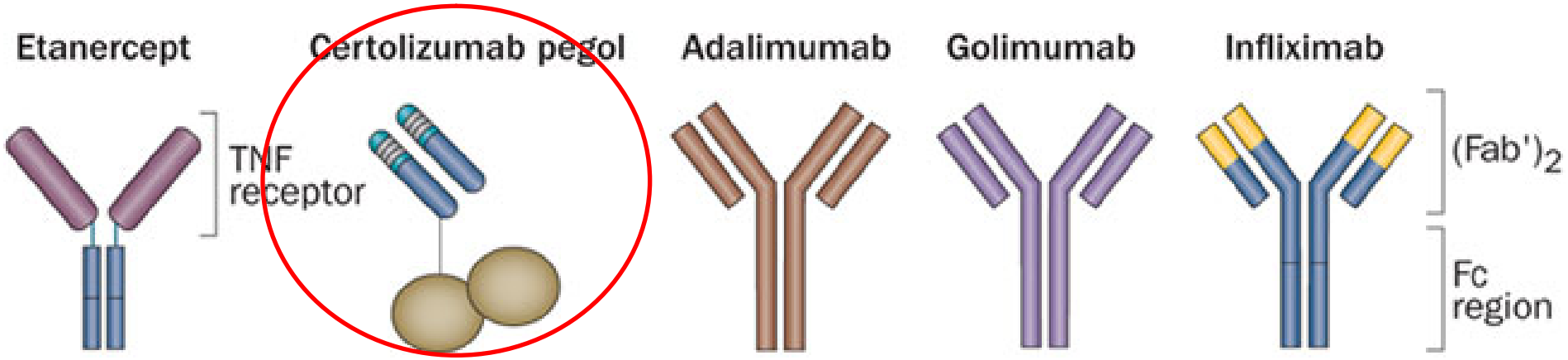


Il trattare la madre nel II trimetre può determinare una elevata concentrazione di farmaco nel sangue fetale che supera quella materna nel terzo trimestre

Le immunoglobuline di origine maternal possono persistere nel sangue del neonato fino a sei mesi

Hazes JMW et al. **Rheumatology.** ***2011;50:1955-1968***

Psoriasi & farmaci biologici



100% Human
Human TNFRp75
Fusion protein

Pso e PsA

Pediatric

80% Human
Peg-Humanized
Fab mAb

PsA

100% Human
Human mAb

Pso e PsA

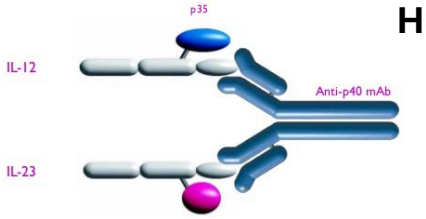
100% Human
Human mAb

PsA

75% Human
Chimeric mAb

Pso e PsA

Ustekinumab

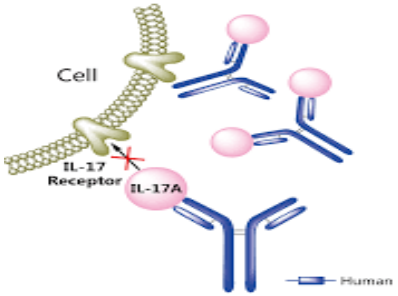


100% Human
Human mAb

Pso PsA

Pediatric

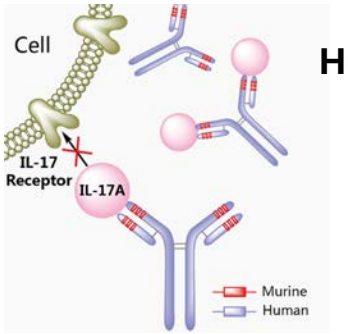
Secukinumab



100% Human
Human mAb

Pso
PsA

Ixekizumab



Humanized
mAb

Pso

Biologici e gravidanza
Passaggio transplacentare

TNFi type	Median percentage of maternal to cord serum level
Infliximab *(complete IgG1 antibody)*	160%
Adalimumab *(complete IgG1 antibody)*	179%
Certolizumab Pegol *(pegylated Fab fragment)*	3,9%
Golimumab *(complete IgG1 antibody)*	-
Etanercept *(fusion protein with Fc part)*	6%

Ostensen M. **Ann N Y Acad Sci** ***2014; 1317: 32–38***

Farmaci anti TNF alpha in gravidanza e rischio neonatale

Esiste un potenziale rischio di infezioni dovuto all'esposione agli anti-TNF alpha durante il terzo trimentre di gravidanza

Le vaccinazioni nei nati da madri trattate con anti-TNF alpha possono essere effettuate secondo i termini previsti ***tranne che per i vaccini vivi (vaccino per rotavirus e BCG) durante i primi sei mesi di vita***

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation

Recommendation

Pregnancy

Drug	Statement on compatibility of drug with pregnancy based on evidence	Percentage of agreement with statement
Infliximab	Current evidence indicates no increased rate of congenital malformations; infliximab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy	100
Adalimumab	Current evidence indicates no increased rate of congenital malformations; adalimumab can be continued up to gestational week 20; if indicated, it can be used throughout pregnancy	100
Golimumab	Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy	100
Etanercept	Current evidence indicates no increased rate of congenital malformations; etanercept can be continued up to gestational week 30–32; if indicated, it can be used throughout pregnancy	100
Certolizumab	Current evidence indicates no increased rate of congenital malformations; certolizumab can be continued throughout pregnancy	100

Götestam Skorpen C, *et al*. *Ann Rheum Dis* 2016;**0**:1–16.

J Am Acad Dermatol. 2012 Sep;67(3):459-77. doi: 10.1016/j.jaad.2011.07.039. Epub 2011 Oct 22.

Review of treatment options for psoriasis in pregnant or lactating women: from the Medical Board of the National Psoriasis Foundation.

Bae YS[1], Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Young M, Bebo B Jr, Kimball AB; National Psoriasis Foundation.

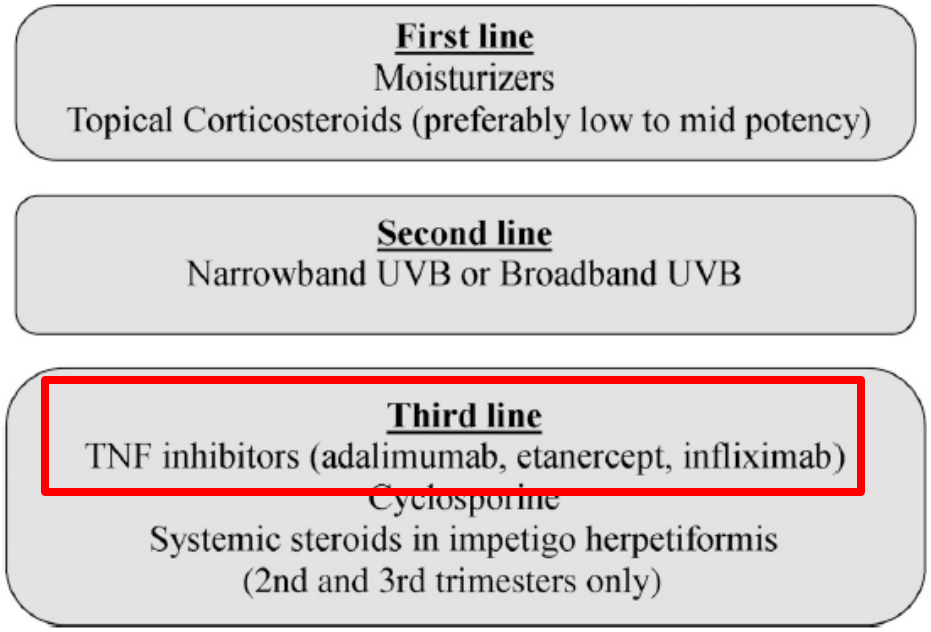


Fig 1. Pregnancy treatment algorithm. *TNF*, Tumor necrosis factor; *UV*, ultraviolet.