Biologics in pregnancy

Fabrizio Conti

Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Direttore Prof. G. Valesini
Agenda

1. Biological drugs before pregnancy: effect on female and male fertility
2. Biological drugs and pregnancy outcome
3. Biological drugs and breast-feeding

The majority of available data concerns TNFi
**Effect of TNF on fertility**

**Female**
- TNF plays a role in the proliferation of normal endometrium and implantation. *Boomsma CM et al. 2009*
- Higher TNF levels in female with endometriosis and infertility. *Younis A et al. 2014, Malutan AM et al. 2015*

**Male**
- Higher TNF concentrations in seminal fluid in infertile male.
- TNF: adverse effects on spermatogenesis, reduction in sperm motility, inhibition of germ cell apoptosis. *Perdichizzi A et al. 2007*

**Treatment with Adalimumab (Humira®) and Intravenous Immunoglobulin Improves Pregnancy Rates in Women Undergoing IVF**

*Treatment with Adalimumab (Humira®) and Intravenous Immunoglobulin Improves Pregnancy Rates in Women Undergoing IVF*

Edward E. Winger¹, Jane L. Reed¹, Sherif Ashoush², Sapna Ahuja², Tarek El-Toukhy², Mohamed Taranissi²

*Treatment with Adalimumab (Humira®) and Intravenous Immunoglobulin Improves Pregnancy Rates in Women Undergoing IVF*

American Journal of Reproductive Immunology 61 (2009)

**Infliximab may reverse the toxic effects induced by tumor necrosis factor alpha in human spermatozoa: an in vitro model**

*Treatment with Adalimumab (Humira®) and Intravenous Immunoglobulin Improves Pregnancy Rates in Women Undergoing IVF*

Fertil. Steril® 2005

Tamer M. Said, M.D.¹, Ashok Agarwal, Ph.D., HCLD.¹,² Tommaso Falcone, M.D.¹,²
Rakesh K. Sharma, Ph.D.¹,²,³ Mohamed A. Bedaiwy, M.D.,¹ and Liang Li, Ph.D.¹
IgG class antibodies are actively transfer across the placenta via their Fc portion binding specialized neonatal Fc receptors (FcRn) on syncytiotrophoblasts (starting from the beginning of second trimester).
TNFi and the other currently licensed biologic drugs for use in rheumatic diseases have an antibody structure.

All biologics containing the Fc portion of IgG are actively transferred through the placenta by fetal Fc receptors expressed in the syncytiotrophoblast. The pegilated Fab’ - Certolizumab Pegol - is not actively transported lacking the Fc portion.

Hyrich & Verstappen. Rheumatology 2014
Østensen M. Ann NY Acad Sci 2014
Bazzani C et al. RMD Open 2015
31 pregnant women with IBD receiving IFX (n=11), ADA (n=10), or CZP (n=10). Serum concentrations of the drugs were measured at birth in the mother, infant, and in cord blood, and then monthly in the infant until the drugs were undetectable.

**INF:** median ratio of cord to maternal drug level 160%. Infant levels were detectable up to 7 months.

**ADA:** median ratio of cord to maternal ADA level 179%. Infant levels were detectable for at least 11 weeks.

**CZP:** no or minimal amount of PEG (median level being 3.9% of the mothers’ level).

Mahadevan U et al. Clin Gastroenterol Hepatol 2013

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A 40-year-old RA treated with ETA during the pregnancy. Ratio of cord to maternal ETA 1/30.


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<table>
<thead>
<tr>
<th>Days post partum</th>
<th>Maternal serum</th>
<th>Breast milk</th>
<th>Child serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>–7</td>
<td>640</td>
<td>540</td>
<td>40°C</td>
</tr>
<tr>
<td>0</td>
<td>–</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

ETA.

Berthelsen BG et al. Rheumatology 2010

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A 34-year-old RA treated with ETA. Ratio of cord to maternal ETA 1/14.
Agenda

1. Biological drugs before pregnancy: effect on female and male fertility
2. Biological drugs and pregnancy outcome
3. Biological drugs and breast-feeding
Anti-TNFα Therapies Are Safe During Pregnancy in Women with Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Nneoji Nnula, MD,* Raed Al-Dabbagh, MD,* Amit Dhillion, MBBS,† Bruce E. Sands, MD, MS,‡ and John K. Marshall, MD, MSc§

Inflamm Bowel Dis • Volume 20, Number 10, October 2014

Gastroenterologist’s perspective

5 studies with a total of 1216 participants (411 on TNFi).
Outcome on TNFi versus controls not receiving TNFi.

TNFi during pregnancy do not increase the overall rate of pregnancy-related unfavorable outcomes.

Forest plot of studies assessing unfavorable pregnancy-related outcomes.
CONSENSUS STATEMENT

The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy

Geoffrey C. Nguyen,1,* Cynthia H. Seow,2,* Cynthia Maxwell,3 Vivian Huang,4 Yvette Leung,5 Jennifer Jones,6 Grigoris I. Leontiadis,7 Frances Tse,7 Uma Mahadevan,8 and C. Janneke van der Woude,9 on behalf of the IBD in Pregnancy Consensus Group

Clinical Practice Guidelines for Inflammatory Bowel Disease in Pregnancy

Statement 10A. In pregnant women with IBD on anti–tumor necrosis factor (TNF) maintenance therapy, we recommend continuation of anti-TNF therapy. GRADE: Strong recommendation, very low-quality evidence. Vote: strongly agree, 42%; agree, 50%; uncertain, 8%.
The British Society for Rheumatology Biologics Register (BSRBR):
✓ **130 pregnancies** in pts who received a TNFi before or during pregnancy:
✓ **88 live births**, 27 of them were born prematurely.

A slight increase in spontaneous abortion rate was observed in women exposed to TNFi at conception (24%), mainly in those also receiving concomitant MTX or LEF (33%).

*Verstappen S et al. Ann Rheum Dis 2011*
The company safety database for pregnancies through to Sept 1, 2014.

339 maternal exposure pregnancies with known outcomes, 226 from prospective studies and 113 from retrospective reports: Crohn disease (192) and rheumatic diseases (118).

Almost all reported pregnancies had exposure to CZP in the first trimester, a third of them continued the drug into the second and/or third trimesters, 41 pregnancies were exposed to CZP in all 3 trimesters.

254 live births (74%),
52 miscarriages (15%),
32 induced abortions,
1 stillbirth.

8 congenital malformation in the prospective cohort (4.3%)
Prospectively-followed pregnancies in patients with inflammatory arthritis taking biological drugs: an Italian multicentre study

C. Bazzani1, R. Scrivo2, L. Andreoli1,3, E. Baldissera4, M. Biggioggero5, V. Canti4, M. Gerosa5, I. Pontikaki5, V. Ramoni6, L. Trespidi7, S. Zatti8, R. Caporali6, R. Gorla1, F. Iannone9, A. Lojacono3,8, P. Meroni5, C. Montecucco6, M. Motta10, M.G. Sabbadini4, G. Valesini2, A. Tincani1,3

79 pregnancies in 67 women affected by different rheumatic diseases (1999 - 2013).

56 ETA, 13 ADA, 3 IFX, 2 CZP, 2 RTX, 1 GOL, 1 ABA, 1 anakinra.

Biologics stopped after a mean of 41 days (range 13-259) since the last period.
The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation


**Characteristics of studies and outcome of pregnancy exposure related to TNFi**

**SLR-period 2008–2015**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type of publication in numbers</th>
<th>References on cohorts and case controls</th>
<th>Total pregnancies† (prospective/retrospective)</th>
<th>Number of miscarriages of eligible pregnancies‡ (%)</th>
<th>Number of congenital malformations of live births§ (%)</th>
<th>Comments on miscarriages (MC) and/or congenital malformations (CM) compared with control groups and/or background data§</th>
<th>Strength of evidence according to GRADE Oxford</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TNF inhibitors, including studies not differentiating between them</td>
<td>10 cohorts (3 abstracts) 5 case controls (1 abstract) 2 register data (1 abstract) 32 case reports/series (7 abstracts)</td>
<td>16 27 36 56–68</td>
<td>2492 (1734/758)</td>
<td>265/2258 (11.7)</td>
<td>75/2110 (3.6)</td>
<td>No difference in MC or CM in pregnancies exposed to TNF inhibitors compared with controls</td>
<td>+++ 2b</td>
</tr>
</tbody>
</table>
Several reports, including systematic literature reviews: collective evidence from many hundreds of pregnancies in IBD and inflammatory arthropathies suggests that exposure to TNFi at the time of conception or during pregnancy does not result in an increased risk of adverse pregnancy and fetal outcomes.

Caution in the use of TNFi in late pregnancy

There is **a potentially increased risk of infections** in the newborn due to TNFi exposure during the third trimester.

*Cheent K et al. J Crohns Colitis 2010*

**PIANO Registry** (1289 women, 1097 completed pregnancy, 1039 with live births) **422 women exposed to a biologic in T3:**
exposure to **TNFi in the third trimester was not associated with increased infant infection** rates at month 4, 9, and 12.

*Mahadevan U et al. Gastroenterology (Suppl. 1) 2014*

Vaccination of **infants exposed to biological therapy in utero** should be given at standard schedules, except for **any live vaccines for the first 6 months of life.**

*Mahadevan U et al. Am J Gastroenterol. 2011*
*Soh & Nelson-Piercy. Rheumatology 2015*
*Nguyen CG et al. Gastroenterology 2016*
The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation


Follow up of children exposed to TNFi in 2nd and/or 3rd trimester of pregnancy

SLR period 2006-2015

<table>
<thead>
<tr>
<th>Maternal medication in pregnancy</th>
<th>Type of publication in numbers</th>
<th>References</th>
<th>Number of children</th>
<th>Mean follow up time and range: years (yrs)</th>
<th>Number of children vaccinated(^1)/children with normal vaccination response</th>
<th>Rate of serious infection(^2) in 1(^{st}) year of life compared to non-exposed children</th>
<th>Physical development: Number of children normal/impaired</th>
<th>Cognitive development: Number of children normal/impaired</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>2 cohorts (2 abstracts) 2 case-controls 7 case-reports</td>
<td>[1-11]</td>
<td>269</td>
<td>1.1 (4 mo.-3yrs)</td>
<td>49/48</td>
<td>Not increased</td>
<td>57/0</td>
<td>22/0</td>
<td>1 child died after BCG vaccination at 3 months of age</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>2 cohorts (2 abstracts) 2 case-controls 3 case-reports</td>
<td>[1,4,7-9,12,13]</td>
<td>136</td>
<td>1.2 (5 mo.-2.2 yrs)</td>
<td>3/3</td>
<td>Not increased</td>
<td>15/1</td>
<td>3/0</td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>2 cohorts (2 abstracts)</td>
<td>[7,8]</td>
<td>99</td>
<td>Not reported</td>
<td>Not increased</td>
<td>10/0</td>
<td>Not studied</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Supplementary Table S7
The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation


<table>
<thead>
<tr>
<th>Drug</th>
<th>Statement on compatibility of drug with pregnancy based on evidence</th>
<th>Percentage of agreement with statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>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</td>
<td>100</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>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</td>
<td>100</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Current evidence does not indicate an increased rate of congenital malformations; because of limited evidence, alternative medications should be considered for treatment throughout pregnancy</td>
<td>100</td>
</tr>
<tr>
<td>Etanercept</td>
<td>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</td>
<td>100</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Current evidence indicates no increased rate of congenital malformations; certolizumab can be continued throughout pregnancy</td>
<td>100</td>
</tr>
</tbody>
</table>
TNFi treatment in men at the time of conception does not increase the risk of any adverse pregnancy outcomes (~120 cases of paternal exposure to TNFi).

<table>
<thead>
<tr>
<th>N° pregnancies</th>
<th>Documented outcome</th>
<th>Drug</th>
<th>Healthy newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kats 2004</td>
<td>15</td>
<td>IFX</td>
<td>9 (1 miscarriage)</td>
</tr>
<tr>
<td>Barcelo 2009</td>
<td>7</td>
<td>ADA/IFX</td>
<td>6 (1 cordial asphyxia)</td>
</tr>
<tr>
<td>Pashou 2007</td>
<td>6</td>
<td>IFX</td>
<td>6</td>
</tr>
<tr>
<td>Viktil 2009</td>
<td>27</td>
<td>none</td>
<td>ADA/ETA not reported</td>
</tr>
<tr>
<td>Clowse 2015</td>
<td>46</td>
<td>CZP</td>
<td>27 (4 miscarriages, 1 elective termination, 1 stillbirth)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rituximab and pregnancy

RTX global drug safety database
preconceptional or
antepartum exposure

90 pregnancies (60%) live births (RA 29, SLE 11)
21% miscarriage (I trimester)
18% elective termination

Full-term delivery 76%
Pre-term delivery (<37w) 24%
Congenital abnormalities 2.2%
Hematological abnormalities 12%
Perinatal infections 4.4%
Pregnancy data on ABA-exposed patients from company safety database that includes clinical trial data and post-marketing reports (1995-2014).

**161 pregnancies** (100 cases prospectively, 61 retrospectively) with known outcomes: 151 cases maternal and 10 paternal exposure.

Any pattern of congenital anomalies
Tocilizumab and pregnancy

RCT: 33 pregnancies in 32 patients

18% TCZ monotherapy
82% TCZ + MTX

Elective termination in 39%
Miscarriage in 21% (of those 71% received concomitant MTX)
Live births in 40%
No congenital abnormalities

Rubert-Roth A et al. ACR 2010

Tocilizumab and pregnancy: Four cases of pregnancy in young women with rheumatoid arthritis refractory to anti-TNF biologics with exposure to tocilizumab

Kayoko Kaneko, Maki Sugitani, Mikako Goto, and Atsuko Murashima

Mod Rheumatol, 2016
The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation


### Points to consider for use of biologics in pregnancy

<table>
<thead>
<tr>
<th>Points to Consider</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ <strong>Continuation of TNFi during the first part of pregnancy should be considered.</strong> Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.</td>
<td>B</td>
</tr>
<tr>
<td>✓ <strong>bDMARDs rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab</strong> have limited documentation on safe use in pregnancy and <strong>should be replaced before conception</strong> by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.</td>
<td>D</td>
</tr>
</tbody>
</table>
Agenda

1. Biological drugs before pregnancy: effect on female and male fertility
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TNF-inhibitors

LOW-RISK MEDICATIONS DURING LACTATION

Little IgG1 amount is present in breast milk, and most available TNFi are based on or contain parts of IgG1 constructs.

All TNFi are high molecular weight proteins → poor diffusion into breast milk.

TNFi → may be broken down by enzymatic degradation in the infant gastrointestinal system.

Sammaritano & Bermas. Curr Opin Rheumatol 2014
Kavanaugh A et al. Arthritis Care Res 2015
INF is excreted in breast milk, albeit at miniscule amounts.

*Ben-Horin S et al. J Crohns Colitis 2011*

The levels of TNFi in breast milk significantly lower than in the maternal circulation.

### 34-year-old pt with AS. ETA (ng/ml) in maternal serum, breast milk, and child serum

<table>
<thead>
<tr>
<th>Days post partum</th>
<th>+40</th>
<th>+41</th>
<th>+42</th>
<th>+43</th>
<th>+44</th>
<th>+45</th>
<th>+46</th>
<th>+47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept, 25 mg s.c.</td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal serum(a)</td>
<td>840</td>
<td>1700</td>
<td>1800</td>
<td>2000</td>
<td>1700</td>
<td>1400</td>
<td>1450</td>
<td>1250</td>
</tr>
<tr>
<td>Breast milk(b)</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Child serum(a)</td>
<td>&lt;4</td>
<td>&lt;4</td>
<td>&lt;4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Berthelsen BG et al. Rheumatology 2010*
**Points to consider for use of biologics during lactation**

<table>
<thead>
<tr>
<th>Points</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Low transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. <strong>Continuation of TNFi should be considered compatible</strong> with breast feeding.</td>
<td>D</td>
</tr>
<tr>
<td>✓ bDMARDs with no data on breast feeding such as <strong>rituximab, anakinra, belimumab, ustekinumab, tocilizumab and abatacept should be avoided</strong> during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs, lactation should not be discouraged when using these agents, if no other options are available.</td>
<td>D</td>
</tr>
</tbody>
</table>
TNFi do not seem to reduce female and male fertility. Several reports, including systematic literature reviews and meta-analysis, suggest that TNFi do not increase the risk of any adverse pregnancy outcomes.

Women who inadvertently become pregnant while taking TNFi should be reassured that continuation of pregnancy does not represent a risk of negative obstetric or neonatal outcomes.

TNFi treatment in men at the time of conception does not increase the risk of unfavorable outcomes in pregnancy.

TNFi considered compatible with breast-feeding.