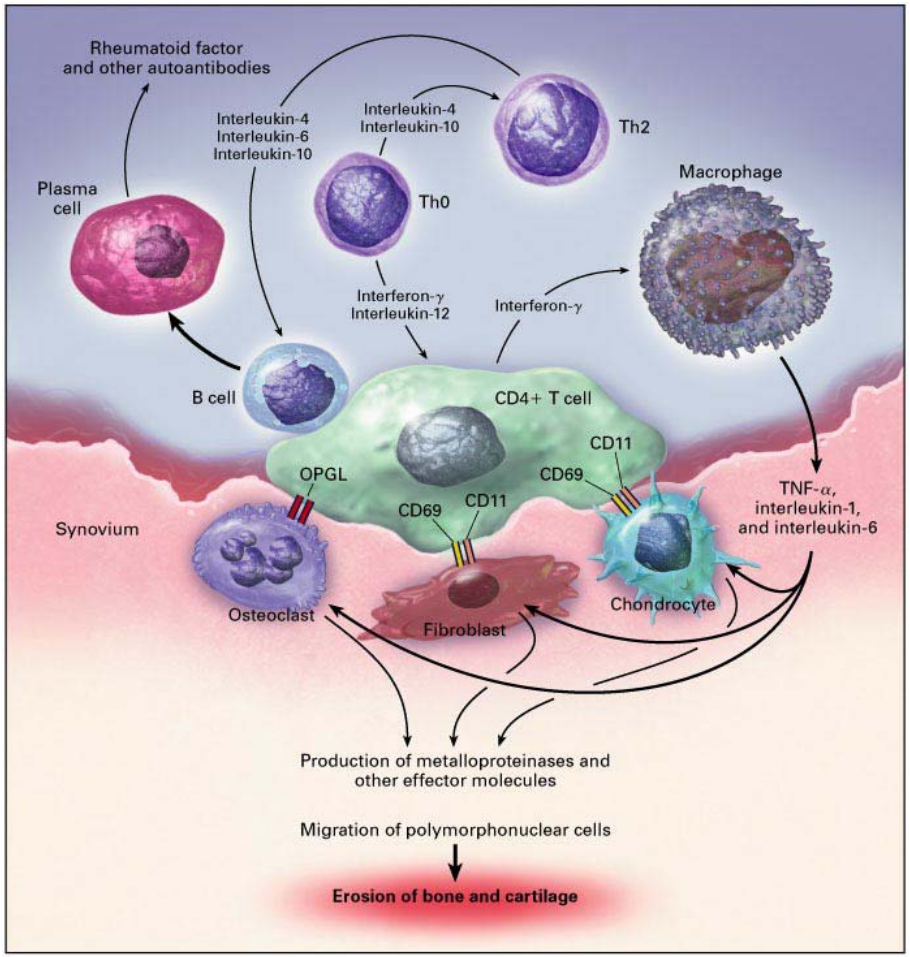
# Biologics in Pregnancy

Dr. Kimme Hyrich
Reader and Honorary Consultant in Rheumatology
Arthritis Research UK Epidemiology Unit
University of Manchester

# Biologic Therapy

- Treat disease by inducing, enhancing, or suppressing an immune response
- Engineered to target specific cells or molecules
- Used in a number of conditions
  - Autoimmune diseases
  - Cancer
- Profound impact on treatment outcomes
- Significant pharmacoeconomic issues

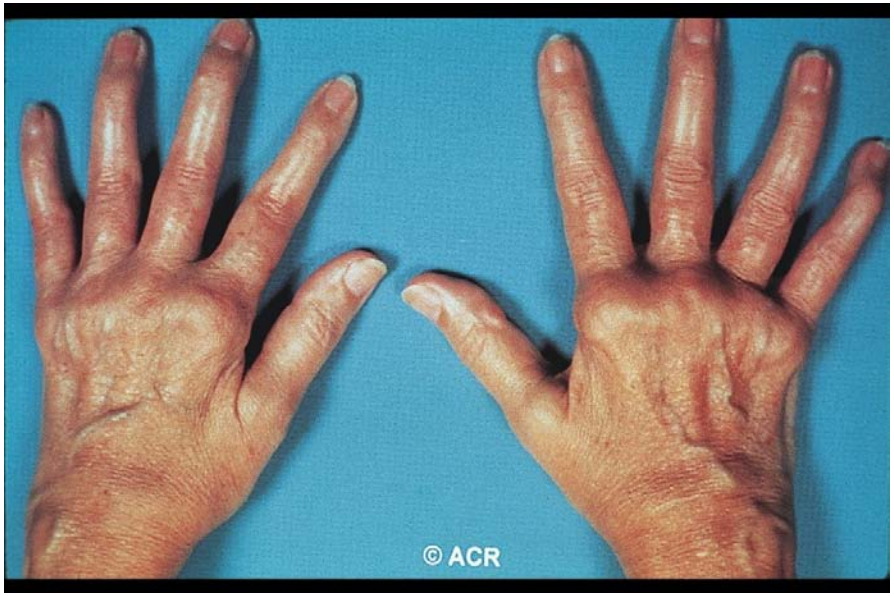
# Cytokine Signalling Pathways in Rheumatoid Arthritis




From Choy and Panayi. NEJM, 2001

# Approved Biologic Therapies in Rheumatoid Arthritis

- Anti-cytokine Therapies
  - TNF
  - IL-1
  - IL 6
- B-Cell Targeted Therapies
  - CD20
- T-Cell Targeted Therapies
  - CTLA4
- Tyrosine Kinase Inhibitors (no routine clinical experience)



# Approved Biologics for Other Autoimmune Diseases

- Inflammatory Bowel Disease
  - Anti-TNF
- Psoriasis
  - Anti-TNF
  - Anti IL 12/23 (ustekinumab)
- SLE
  - B-cell Activating Factor (BAFF) inhibitors
- Multiple Sclerosis
  - Anti-α4-integrin (natalizumab)
  - Interferon-beta

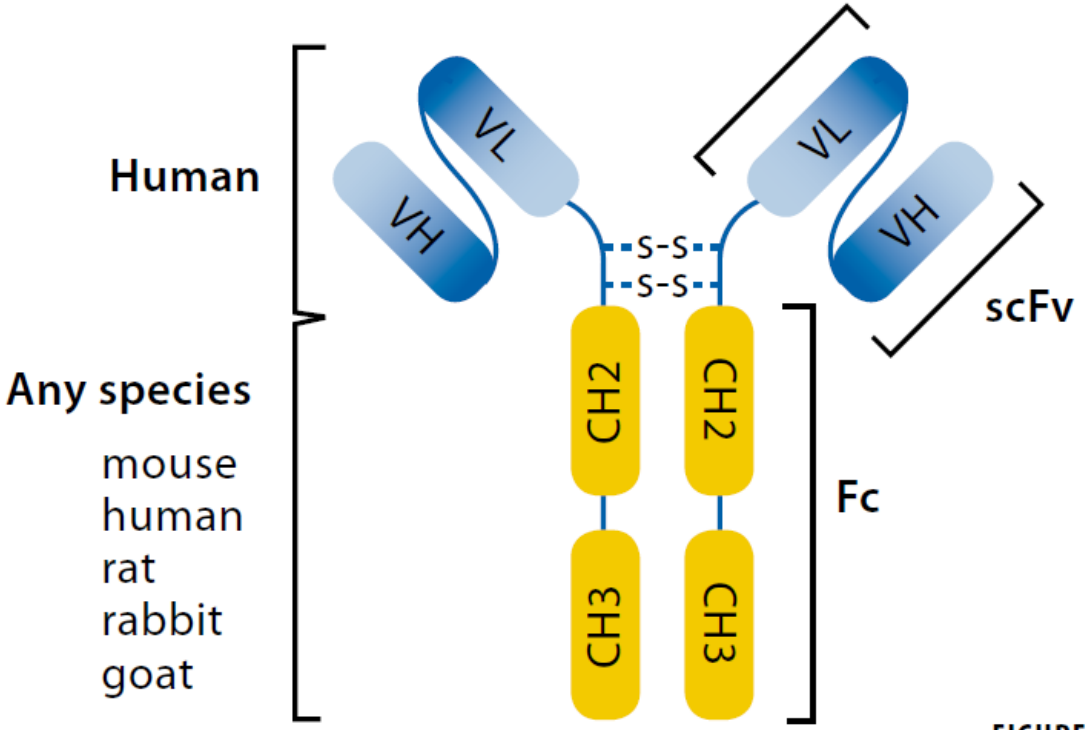



**FIGURE:** Structure of Recombinant Antibodies

From http://www.adipogen.com

# Nomenclature

| | |
|---|---|
| – ximab | chimeric antibody |
| | eg. infliximab |
| – umab | human antibody |
| | eg. adalimumab |
| – zumab | humanised antibody |
| | eg. tocilizumab |
| – cept | fusion protein |
| | eg. etanercept |

# Biologics in Pregnancy

- Anti-TNF
- Anti-CD20 (rituximab)
- Anti-IL6 (tocilizumab)

# Biologics in Pregnancy

- Anti-TNF
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# Anti-TNF Therapies

- Over 10 years experience in rheumatology, gastroenterology and dermatology

- Rheumatology
  - Rheumatoid arthritis
  - Psoriatic arthritis
  - Ankylosing spondylitis
  - Juvenile idiopathic arthritis

- Gastroenterology
  - Inflammatory bowel disease

- Dermatology
  - Psoriasis

# Approved Monoclonal Anti-TNF Agents

## Infliximab (Remicade®)

- Chimeric monoclonal IgG1 antibody
- IV 8 weekly

## Adalimumab (Humira®)

- Human monoclonal IgG1 Ab
- SC fortnightly

## Golimumab (Symponi®)

- Human monoclonal IgG1 Ab
- SC monthly

## Etanercept (Enbrel®)

- Recombinant soluble p75 TNF receptor: Fc fusion protein
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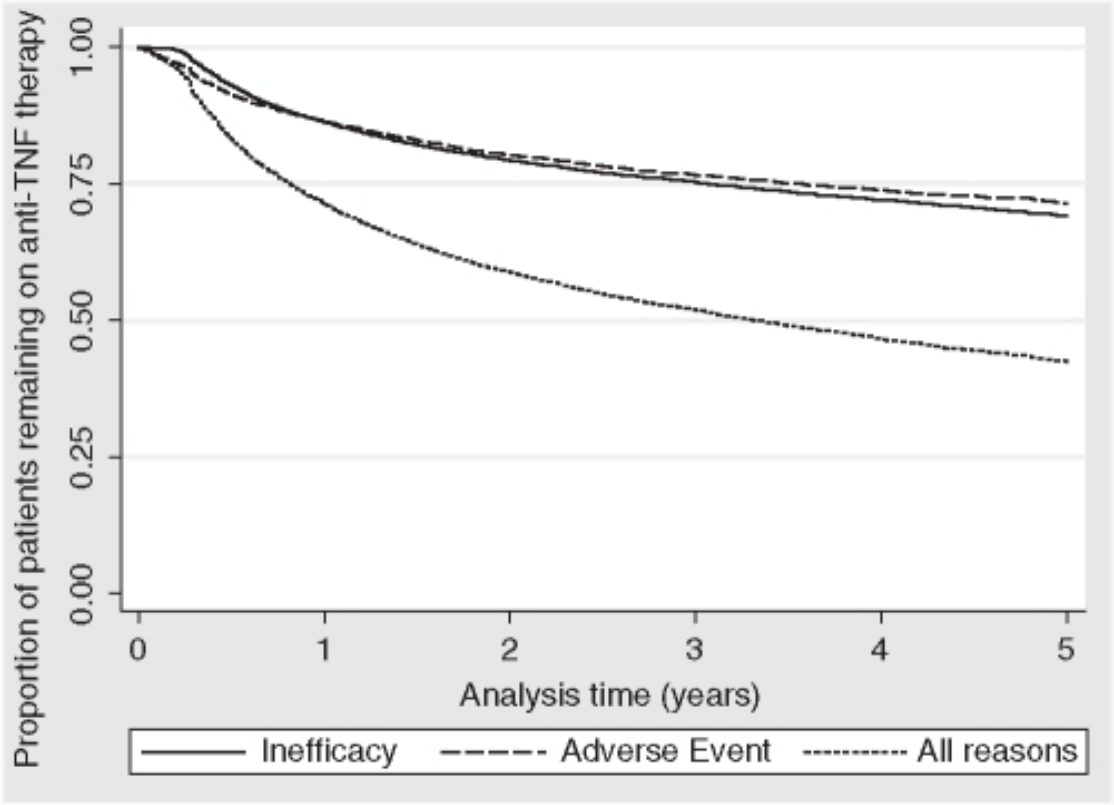
# Effectiveness of Anti-TNF Therapies




Soliman et al. Ann Rheum Dis, 2011

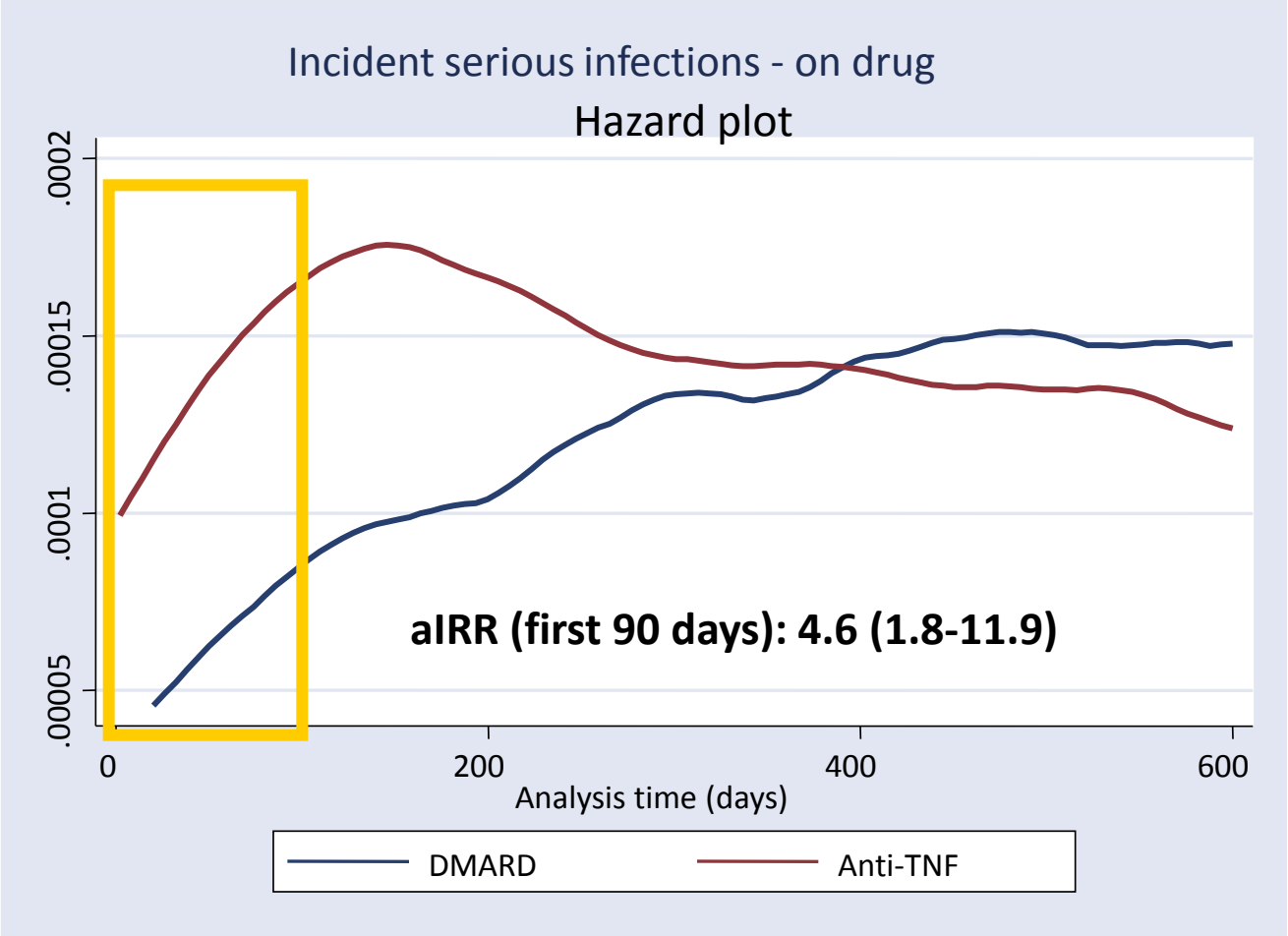
# Anti-TNF Therapies

Maternal Risk

# TNF and Infection

- Plays a crucial role in body's defence against bacterial and viral invasion
- Acute phase response
  - Inflammatory cell recruitment
  - Release of local cytokines and chemokines
  - Attraction and stimulation of phagocytes
  - Enhanced antigen presentation
  - Recruitment of T and B lymphocytes
- Important in formation and maintenance of granulomas

# Risk of Serious Infection




Dixon et al. Arthritis and Rheumatism, 2007

# Anti-TNF Therapies and Risk of TB

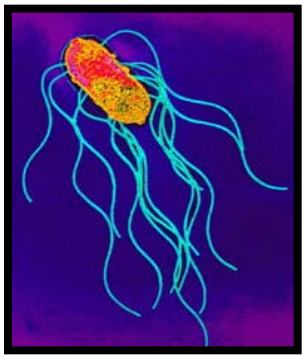
Spanish Infliximab Register

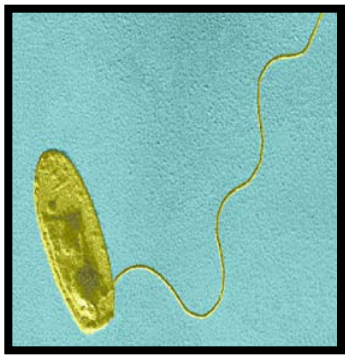
- RR (Spanish population) 90.1 (95% CI 58.8-146.0)
- RR (Rheumatoid Arthritis) 11.7 (95% CI 9.5-14.6)

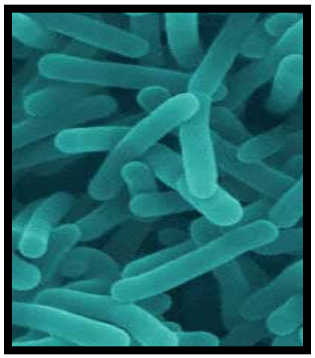
- UK Biologics Register
  - Reports of TB up to one year after stopping anti-TNF therapy

Gomez Reino Arthritis and Rheumatism, 2003; Dixon et al. Ann Rheum Dis, 2010

# Intracellular Bacterial Infections





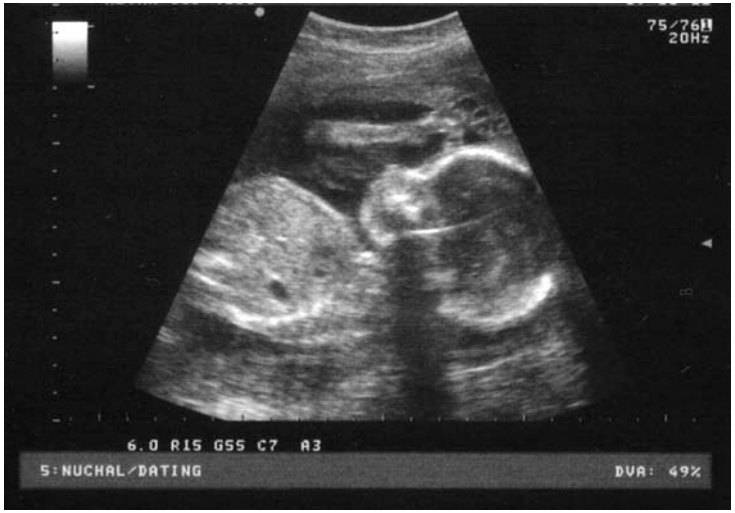


| | Salmonella | Legionella | Listeria |
|---|---|---|---|
| General Population | | 318 cases E+W 2004 | 193 cases E+W 2003 |
| Anti-TNF | Bowel (2)<br>Joint (1)<br>Septicaemia (1) | LRTI (5) | Septicaemia (1)<br>Joint (2)<br>Meningitis (2) |

Data from BSR Biologics Register to 2004

# Public health action

# Anti-TNF Therapies



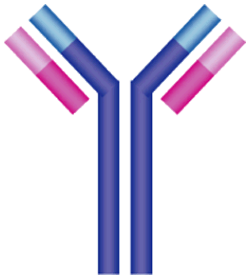

Foetal Risk

# Summary of Product Characteristics (SPC): Anti-TNF and Pregnancy

- Etanercept: wait at least 3 weeks after last dose
- Adalimumab: wait at least 5 months after last dose
- Infliximab: wait at least 6 months after last infusion
- Golimumab: wait at least 6 months after last infusion

From Electronic Medicines Compendium. www.medicines.org.uk (last accessed 19/06/2012)

# Maternal-Foetal Antibody Transfer



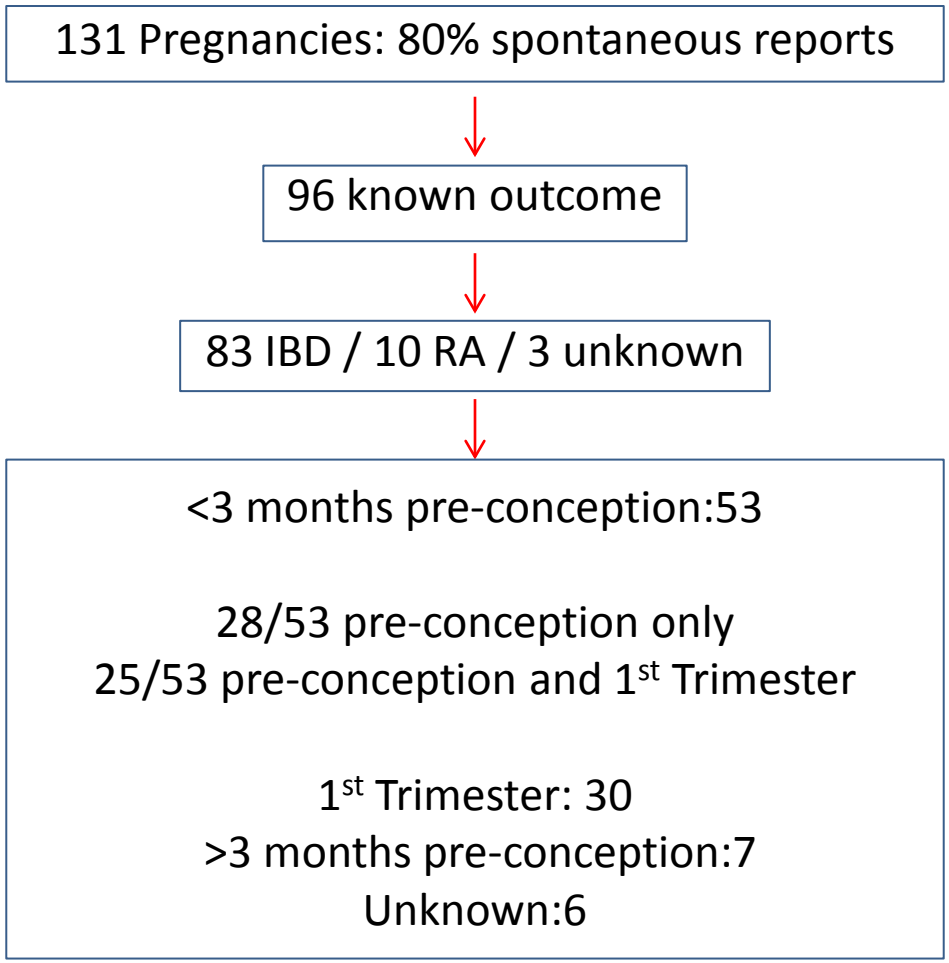
- Most antibodies in newborn are of maternal origin
- Antibodies require active transport across the placenta via Fc receptors as too large for diffusion.
- Fc receptor hardly detectable prior to week 14
- IgG undergo active placental transport beginning in T2 which rapidly increases over T3.
- At term, foetal levels of IgG somewhat exceeds maternal levels

# Levels of Evidence

# The Challenge of Animal Studies of Mab's

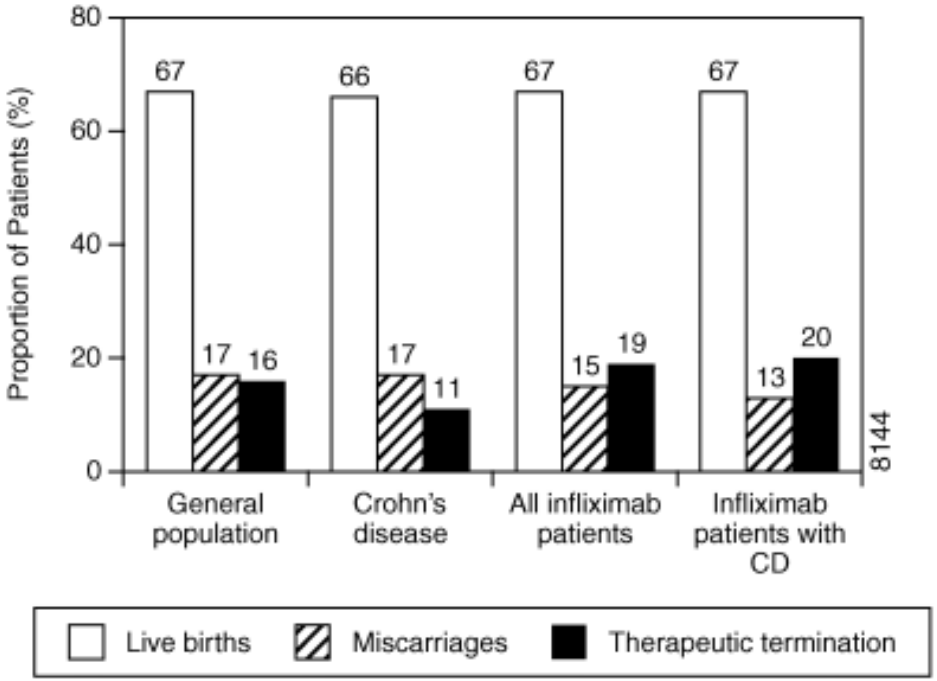
- In general, no concerns raised in pre-clinical animal studies of anti-TNF
- Placental transport of Ab's is species specific
- Studies in Old World monkeys (eg. cynomolgus macaques) felt to best resemble human studies
- Surrogate antibodies in rats or mice also studied

# Centocor Adverse Events Database




Katz et al. Am J Gastro, 2004

# Outcomes of Pregnancy in Women Receiving Infliximab for IBD or Inflammatory Arthritis




Congenital Abnormalities:

Tetralogy of Fallot (1)
Intestinal malrotation (1) – also exposed to leflunomide

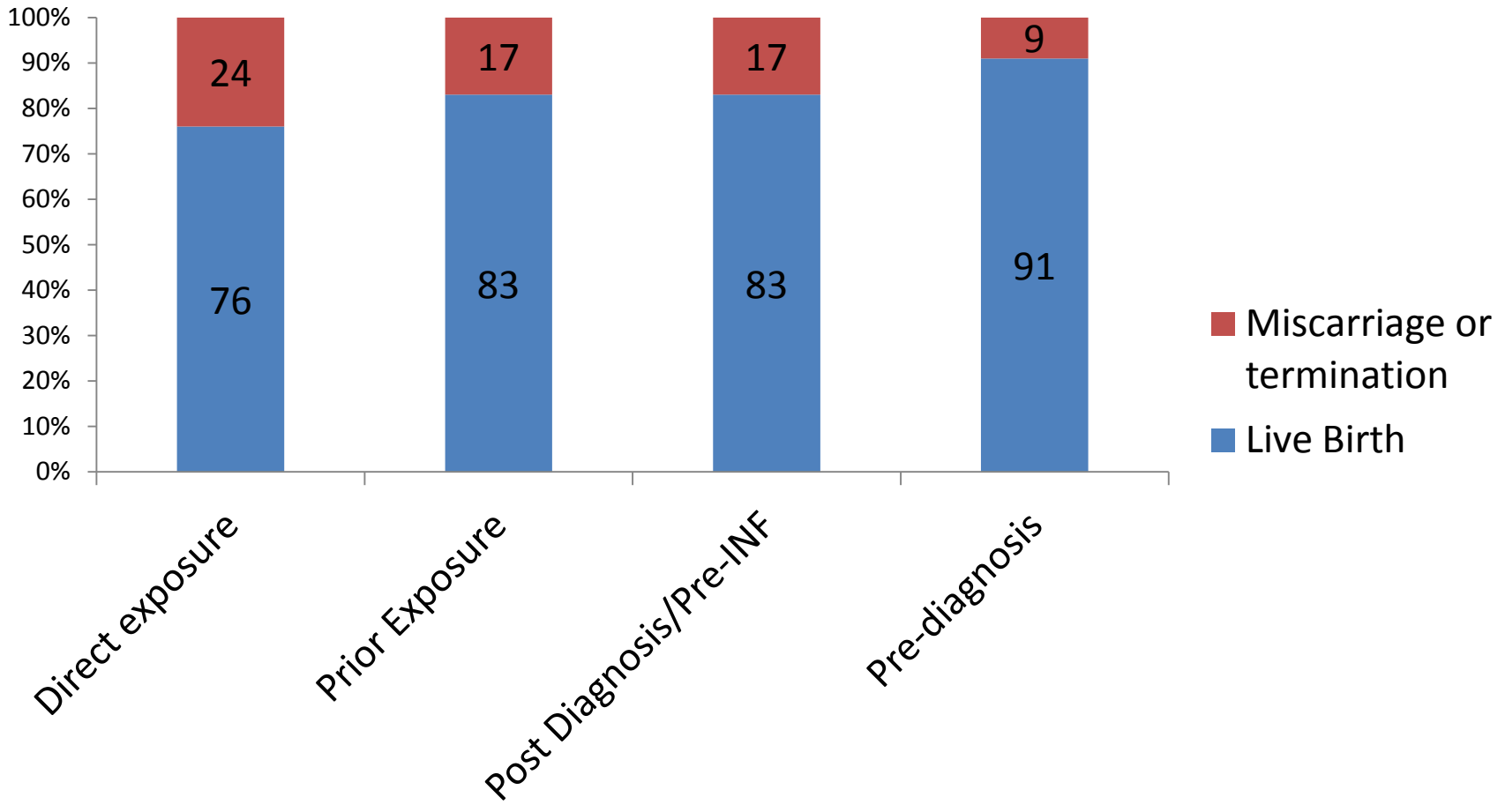
Katz et al. Am J Gastro, 2004

# Further experience in IBD

- 197 pregnancies in IBD clinic
  - 23 prior to diagnosis
  - 78 no exposure to anti-TNF
  - 54 with prior exposure to anti-TNF
  - 42 with direct exposure to INF/ADA
- Direct exposure – within 3 months of conception or during pregnancy

Schnitzler et al. IBD, 2011

# Outcomes of Pregnancies




Schnitzler et al. IBD, 2011

# French Rheumatology Experience to 2006

- French rheumatologists asked to report pregnancies to online database

- 15 pregnancies
  - 3 infliximab, 2 adalimumab, 10 etanercept
  - Majority stopped in 1st trimester
  - 1 patient continued ADA throughout pregnancy (term delivery)

  - 1 miscarriage
  - 2 therapeutic abortions
  - 12 healthy newborns

Berthelot et al. Joint Bone Spine, 2009

# Population Database Record Linkage

*Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150 000 pregnant women and expectant fathers*

- Norway: linked birth registry and prescription database
- All drugs 3 months prior to and during pregnancy
- 37 etanercept and 3 adalimumab
  - 14 – pre-conception/23 - 1st T/ 2 - 2nd T/ 1- 3rd T
  - No birth defects noted

Viktil et al, Scand J Rheumatology, 2012

# BSR Biologics Register

>20000 patients

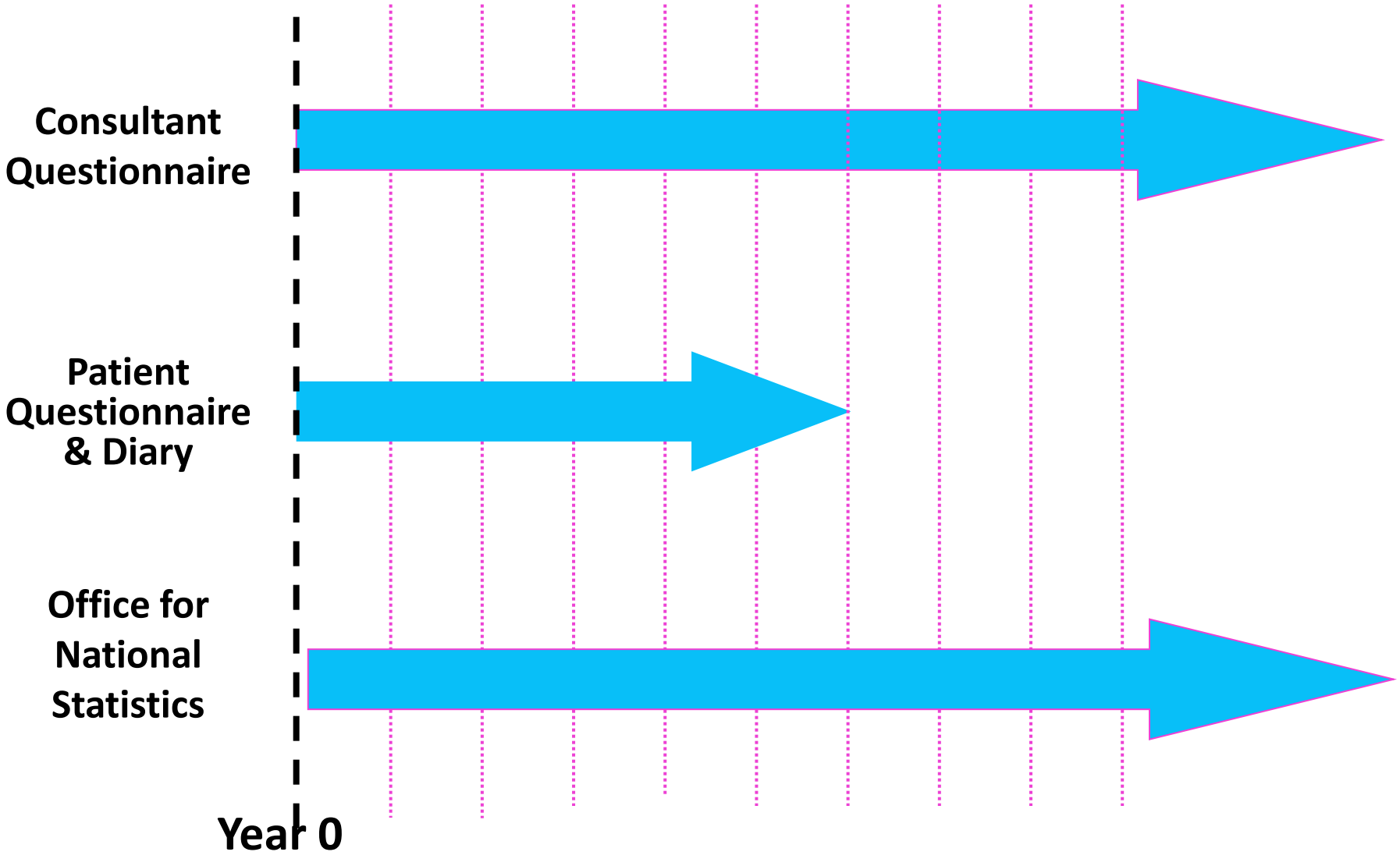
>14000 anti-TNF treated patients

>1500 rituximab treated patients

>3500 DMARD treated patients

75% females, median age 55 years

# BSR Biologics Register



# Outcome in all Pregnancies

| Outcome | Direct Exposure With MTX | Direct Exposure Without MTX | Prior Exposure | Never Exposed |
|---|---|---|---|---|
| **Pregnancies** | 21 | 50 | 59 | 10 |
| **Live Births, %** | 48 | 64 | 78 | 90 |
| **Early miscarriage, %** | 33 | 24 | 17 | 10 |
| **Intrauterine or neonatal death, %** | 0 | 6* | 3* | 0 |
| **Termination, %** | 19 | 8 | 3 | 0 |
| **Birth defects**, n** | 0 | 2 | 2 | 0 |

*Includes a single death in a twin pregnancy in each group

** one each of congenital hip dysplasia, pyloric stenosis, winking jaw syndrome, strawberry nevus

Verstappen et al. Ann Rheum Dis, 2010

# VACTERL Association

- Case report in 2006 of child with VACTERL association

- VACTERL
  - a non-random association of birth defects
  - 3 or more problems usually associated with diagnosis

V - Vertebral anomolies
A - Anal atresia
C - Cardiovascular anomolies
TE – Tracheoesophageal fistula
R - Renal Anomalies
L - Limb defects

Carter et al. J Rheum, 2006.

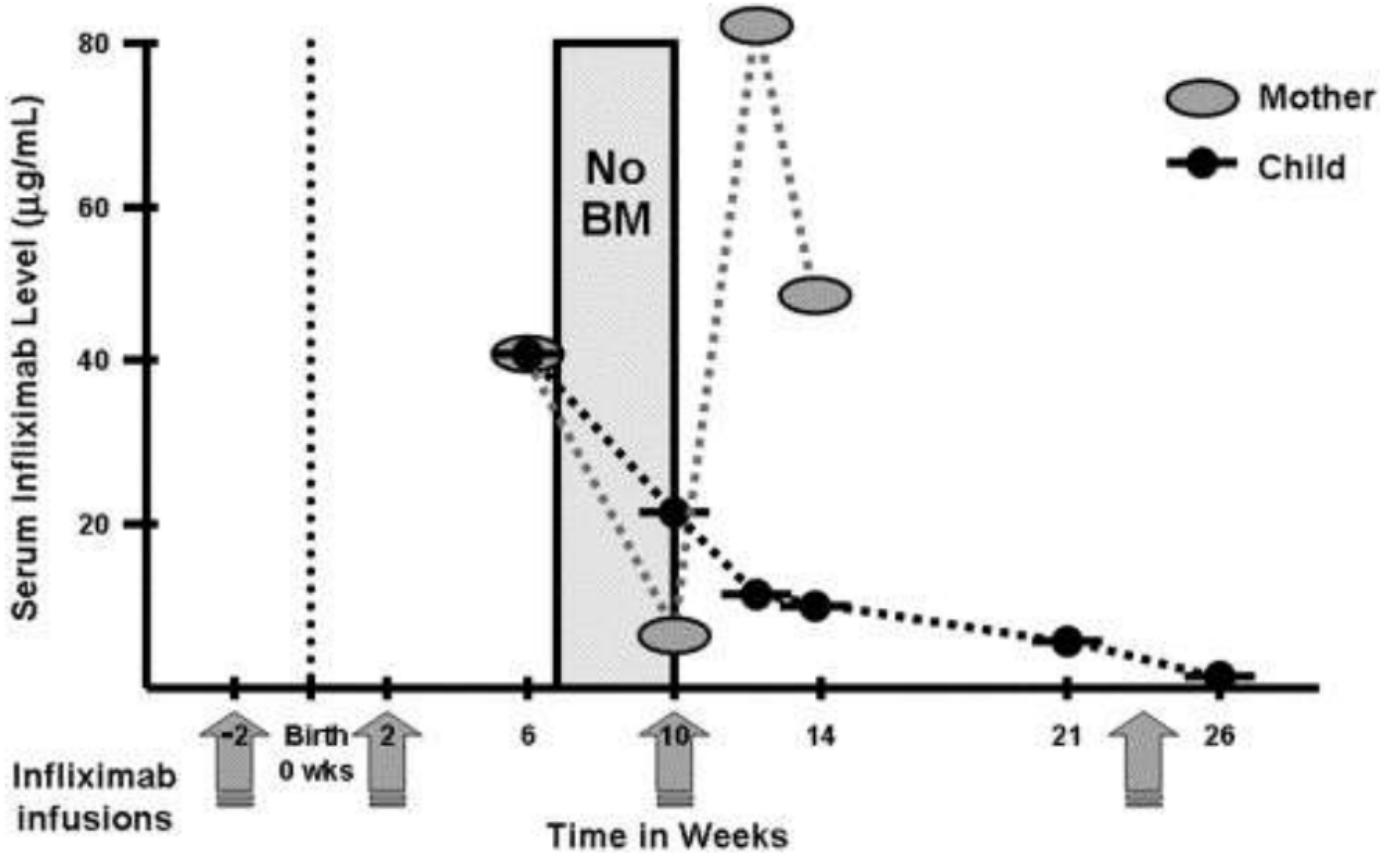
# VACTERL Association

- A review of congenital abnormalities reported to FDA in patients receiving anti-TNF therapy
  - 61 congenital abnormalities in 41 children
  - 19 were part of the VACTERL spectrum
    - The majority only had a single abnormality
    - 7 had 2 within the VACTERL spectrum
    - 1 diagnosed with VACTERL
- Unknown denominator
- Background rate of birth defects: 3-5%

Carter et al. J Rheum, 2009.

# Anti-TNF Therapy and the Newborn Child

# Infliximab Levels in Newborn




From Vasiliauskas et al. Clin Gast Hep , 2006

# Etanercept Levels in Newborn

| Days Post-Partum | -7 | 0 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 |
|---|---|---|---|---|---|---|---|---|---|---|
| Etanercept | X | | X | | | | | | | X |
| Maternal Serum | 640 | 540 | 840 | 1700 | 1800 | 2000 | 1700 | 1400 | 1450 | 1250 |
| Breast Milk | | | 2 | 3 | 4 | 5 | 3 | 4 | 2 | <2 |
| Child serum | | 40* | | <4 | <4 | <4 | | | | |

* Cord Blood

34 yo female with AS continued 25 mg etanercept once weekly throughout pregnancy and breastfeeding

Berthelsen et al. Rheumatology, 2010

# Childhood Vaccination – a warning

- **Case report**
  - 28 yo female with CD received infliximab throughout pregnancy
  - Infant received BCG vaccine at 3 months
  - Infant developed disseminated BCG and died

- Animal studies of immune development and human studies of routine childhood vaccine response normal

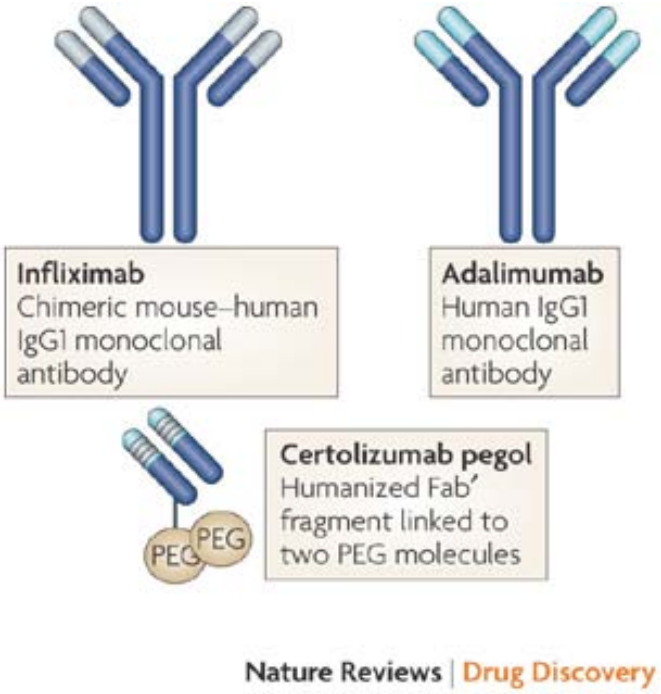
- Suggested to avoid live vaccines during first 6 months of life

Vasiliauskas et al. Clin Gast Hep , 2006. Cheent et al. J Crohns Colitis, 2010.

# CERTOLIZUMAB-PEGOL

# Certolizumab pegol (Cimzia®)

- a PEGylated Fab' fragment of a humanized TNF inhibitor monoclonal antibody




From Melmed et al. Nature Reviews Drug Discovery 7, 641-642 (August 2008)

# Transplacental Transfer of Cert-Peg

- No Fc portion – therefore would not be expected to cross placenta by active transport
- ~80 kD – passive diffusion likely to be minimal as well

| | Structure | Placental Transfer (% of maternal levels in foetus at term) | Excretion in Milk (% of maternal level at day 7) |
|---|---|---|---|
| cTN3 ϒ1 | IgG | 15% | 24% |
| cTN3 PF | PEGylated Fab' | <0.3% | <5% |

*Surrogate antibody study in rats

Wakefield et al. Toxicological Sciences, 2011

# Clinical Experience – Cert Peg

- Single case report
- 22 yo female with Crohn's disease
- Pre-conception, single dose in T1 and in T3 (w31)
- Healthy term infant with normal growth at 1 month

Oussalah et al. Gut, 2009

# Current Manufacturer's Recommendations

- Certolizumab - wait at least 5 months after last dose

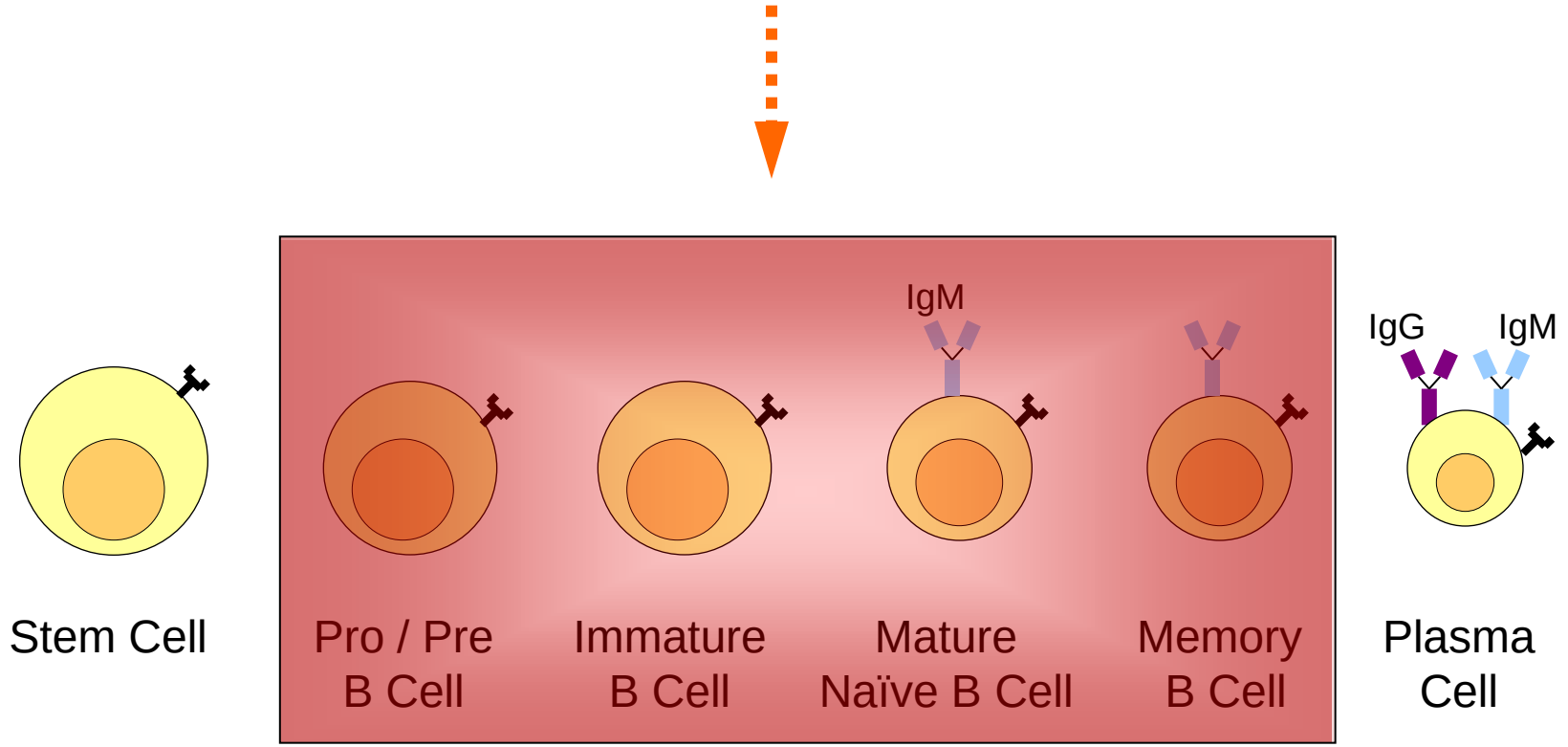
# Biologics in Pregnancy

- Anti-TNF
- Anti-CD20 (rituximab)
- Anti-IL6 (tocilizumab)

# Rituximab (Mabthera®)

- Anti-CD20 monoclonal antibody
- Used as complement to CHOP therapy for B-cell lymphomas
- More recently (2006) approved for use in combination with methotrexate for RA
- Functions through depletion of B-cells

# Rituximab


IgM
IgG
IgM
Stem Cell
Pro / Pre
B Cell
Immature
B Cell
Mature
Naïve B Cell
Memory
B Cell
Plasma
Cell
Bone Marrow
Periphery

# Rituximab and rheumatoid arthritis

- B-cell depletion is rapid and variable
- Can last between 5 and 14 months
- With repeated infusions: 25% have subnormal levels of IgM
- Effects on long-term infection risk unknown

- Current recommendations:

*"Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during treatment and* ***for 12 months following MabThera therapy****"*

European SPC - Mabthera

# Rituximab – Animal Studies

- Cynomolgus monkey studies
  - No embryotoxicity
  - Reduced B cells in infants but returned to normal by 6 mos
  - Normal T-cell response to vaccination
- Small amount of RTX detectable in milk of lactating monkeys
  - 0.19-0.26% of serum levels

Vaidyanathan et al. Toxicological Sciences, 2011

| Author, date | Time of Exposure | Diagnosis | Neonatal condition | B-cell count at birth | B-cell count at follow-up (duration) | Ig levels at birth | Complications during follow-up (duration) | Vaccination response |
|---|---|---|---|---|---|---|---|---|
| Ton, 2011 | Pre | RA | Twins (one clubfoot) | Normal | Normal (8m) | Normal | None | |
| Pellkofer, 2009 | Pre | MS | Healthy term | Normal | Normal | Normal | None (15m) | Normal |
| Kimby, 2004 | Pre and T1 | NHL | Healthy term | Low | Normal (2w) | Normal | None (18m) | Normal |
| Ponte, 2010 | T1 | Atopic Dermatitis | Healthy term | Normal | | | | |
| Ojeda-Uribe, 2006 | T1 | AIHA | Healthy term | Normal | Normal (8w) | Normal | None (6m) | |
| Gall, 2010 | T2 (w 26) | ITP | Healthy term | Low | Normal (4m) | | None (4m) | |
| Herold, 2001 | T2/T3 CHOP | NHL | Healthy, w35 | | Normal (8w) | | None (4m) | |
| Friedrichs, 2006 | T2/T3 CHOP | Lymphoma | Healthy term | Absent | Normal (4m) | | None (26m) | Normal |
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# Biologics in Pregnancy

- Anti-TNF
- Anti-CD20 (rituximab)
- Anti-IL6 (tocilizumab)

# Tocilizumab

- Data limited to patients enrolled in Roche clinical trials (abstract form only)

- 31 pregnancies with known outcome
- Majority occurred “despite” contraception
- 26 had received concurrent MTX therapy
  - 13 therapeutic abortion
  - 7 miscarriages
  - 11 term pregnancies (1 neonatal death at day 3)

Rubbert-Roth et al. A&R, 2009.

# Tocilizumab

- Clinical trial underway to assess pharmacokinetics and pharmacodynamics of hormone contraceptives in women exposed to tocilizumab

# Summary

# Summary – Anti-TNF

- Anti-TNF exposure during pre-pregnancy, at conception and during 1st trimester not associated with reported increased in congenital malformations or adverse pregnancy outcomes
- Exposure 3rd trimester associated with measurable drug in the newborn but varies by drug
- Certolizumab-pegol may be an exception
- Avoidance of live vaccine in exposed neonates
- Advice to stop the drug 3 weeks to 5 months prior to pregnancy not currently supported by published evidence

# Summary - Rituximab

- Crosses placenta in 2nd and 3rd trimester placenta
- Lymphopaenia in newborn
- Pre-pregnancy and early 1st trimester exposure appears to be safe with no consistent teratogenic affects reported
- Advice to stop the drug 12 months prior to conception not currently supported by published evidence

# Summary
# Other Biologics in Autoimmune Diseases

- Experience extremely limited to case reports, clinical trial exposure or animal studies only.
- ?Barrier contraception with tocilizumab
- Further experience is warranted before any specific recommendations can be made.

# Summary

- Long-term effects of biologic exposure in the foetus and neonate remain unknown