*LA CRITICITA' DELLA TERAPIA BIOLOGICA*
*Firenze 29 Novembre 2008*

# TERAPIE BIOLOGICHE E GRAVIDANZA


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# Biologic Agents and Pregnancy

*Therapeutic monoclonal antibodies and other biological agents are used to a greater extent to treat many immuno-mediated disorders in pregant patients.*

***Stengel, World J Gastroenterol, 2008***

# Immuno-mediated disorders and fertile patients

- Bowel inflammatory diseases
- Rheumatoid arthritis
- Systemic Lupus Erythematosus
- Thrombocytopenia
- Multiple Sclerosis
- Myasthenia Gravis
- Antiphospolipid Antibodies Syndrome

# Biologic Agents

- ✓ Intravenous immunoglobulins
- ✓ Monoclonal Antibodies
- ✓ Autologous Hematopoietic Stem Cells

*Rapid developments in biotechnology over the past decade has offered the opportunity to develop a greater understanding of the immunopathogenetic dysregulation… and develop targeted therapy to intefer with this disregulation at various levels…*

***Ioannou, Postgrad med J, 2002***

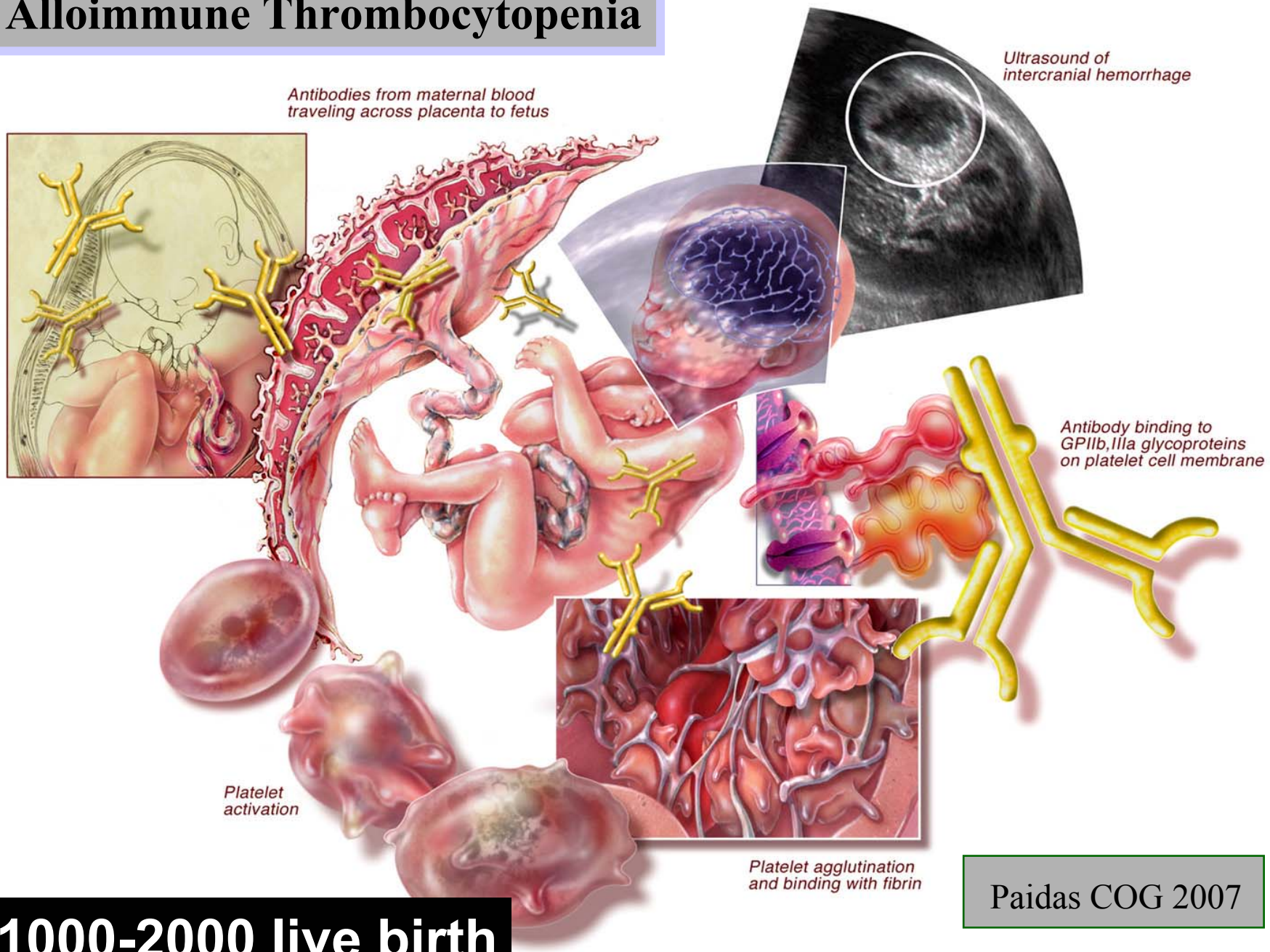
# Biologic Agents

- ✓Intravenous immunoglobulins
- ✓Monoclonal Antibodies
- ✓Autologous Hematopoietic Stem Cells

# Intravenous Immunoglobulin and Pregnancy

1) Fetal-neonatal Alloimmune Thrombocytopenia
2) Fetal-neonatal Alloimmune Hemolysis
3) Recurrent miscarriage
4) Antiphospholipid Syndrome
5) Autoimmune Thrombocytopenia
6) Multiple Sclerosis
7) Myasthenia Gravis

# Alloimmune Thrombocytopenia




1:1000-2000 live birth

Paidas COG 2007

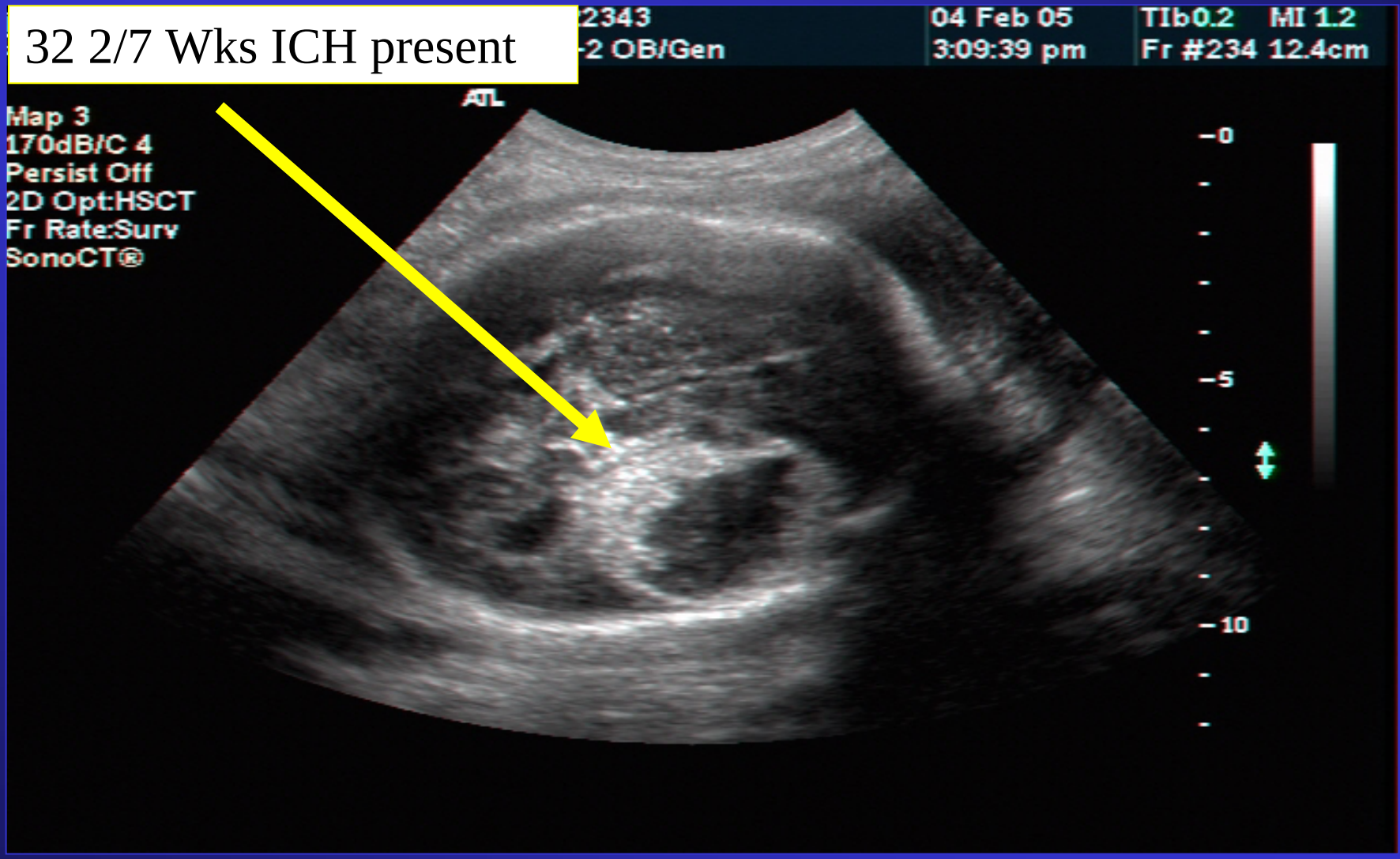
# 1) Alloimmune Thrombocytopenia

Due to Human Platelet Antigen incompatibility (HPA-1a most common)

## Antenatal Ultrasound

- ICH (as early as 14 weeks)
- Hydrocephalus
- Porencephalic cysts

# 1) Alloimmune Thrombocytopenia



# 1) Alloimmune Thrombocytopenia

Due to Human Platelet Antigen incompatibility (HPA-1a most common)

## IVIG Randomized Trial: Results

### Incidence of ICH

| Treated Fetuses | Sibling* |
|---|---|
| 0/55 | 10(19%) |

*3 occurred in utero

# 1) Alloimmune Thrombocytopenia: current protocol

- **Standard risk:** If prior affected child had thrombocytopenia **& no ICH**, options are IVIG 1gram/kg/wk or Prednisone 0.5mg/kg/d. Start at 20 wks.

- **High risk:** If prior affected child had **peripartum ICH**, appropriate therapy includes IVIG 1gram/kg/wk & Prednisone 1mg/kg/day, starting at 20 wks.

- **Very high risk:** If prior affected child had **antenatal ICH**, a more intense prevention strategy is needed: IVIG 2gram/kg/wk starting at 12 wks. Fetal Blood Sampling should be performed at 20 wks. If additional therapy is required, prednisone 1mg/kg/day should be instituted. Finally, weekly in utero platelet transfusion or delivery are last resort.

# 2) Alloimmune Hemolysis

**PERSISTENCE OF FETAL ALLOIMMUNE HEMOLYSIS**

- Small proportion of Rh D-negative become alloimmunized because of failed or forgotten anti-D immune globulin prophylaxis

- Alloimmunization to non-Rh D erythrocytes antigens (RhE, Rhc, RhC, Kell, $Fy^a$)

# 2) Alloimmune Hemolysis

**IVIG**

**Empiric use should be limited to unusually severe cases caracterized by:**

- Antierythrocyte alloimmunization with a history of severe fetal hemolysis in spite of conventional treatment with fetal transfusion

- A history of early-onset severe anemia (< 20 weeks) when fetal transfusion is difficult technically

# 2) Alloimmune Hemolysis

## IVIG

Maternal antibodies synthesis

Blockade of Fc-mediated Antibody placental transport

Limiting fetal red blood cell destruction

# 3) Recurrent Miscarriage

**6 randomized controlled trials**

The use of IVIG in the treatment of recurrent miscarriage should be abandoned

# 4) Antiphospholipid Antibodies

Case series suggests that IVIG may benefit women with APS who have failed heparin treatment in a prior pregnancy.

# 5) Multiple Sclerosis

- IVIG as second line treatment for Relapsing-Remitting MS if conventional immunomodulatory therapies are not tolerated of side effect or concomitant disease

- In pregnancy: where other therapies may not be used

# 6) Myastenia Gravis

- Cochrane reviews concluded that IVIG is a well-documented short-term treatment for acute exarcerbation

- IVIG is widely recommended for severe MG or MG exacerbations during pregnancy and also before delivery (improve the muscle strenght)

# Biologic Agents

- ✓ Intravenous immunoglobulins
- ✓ Monoclonal Antibodies
- ✓ Autologous Hematopoietic Stem Cells

*- Large molecules (>140.000 g/mol)*

*- Hardly pass the placenta during embryogenesis*

*- Maternal IgG tranplacental transfer begins in II trimester and peaks at term*

# Monoclonal Antibodies

## Potential Therapeutical Drugs

| | |
|---|---|
| B CELL interaction drugs | - *Rituximab* (anti CD20)<br>- *Epratuzumab* (anti CD22)<br>- *Belimumab* (anti BLyS) |
| B-T CELLS costimulation interferaction drugs | - Anti CD40<br>- *Abatacept* (CTLA4-Ig) |
| Drugs targeting Cytokines | - *Infliximab* (anti TNFα)<br>- *Etanercept* (anti TNFα)<br>- *Adalimumab* (anti TNFα)<br>- *Trastuzumab* (anti TNFα)<br>- Anti IL-1, IL-6, IL-10 |

# Monoclonal Antibodies and Teratology

*" Available data do not indicate a major teratogenic risk of monoclonal antibodies."*

*..There is evidence for an association of Trastuzumab and oligohydramnios in 2nd and 3rd trimester..*

*"More research is necessary, in particular to evaluate other short and long term effects of exposure to monoclonal antibodies during the second half of pregnancy."*

*C.Weber-Schoendorfer, Reprod Tox 2008*

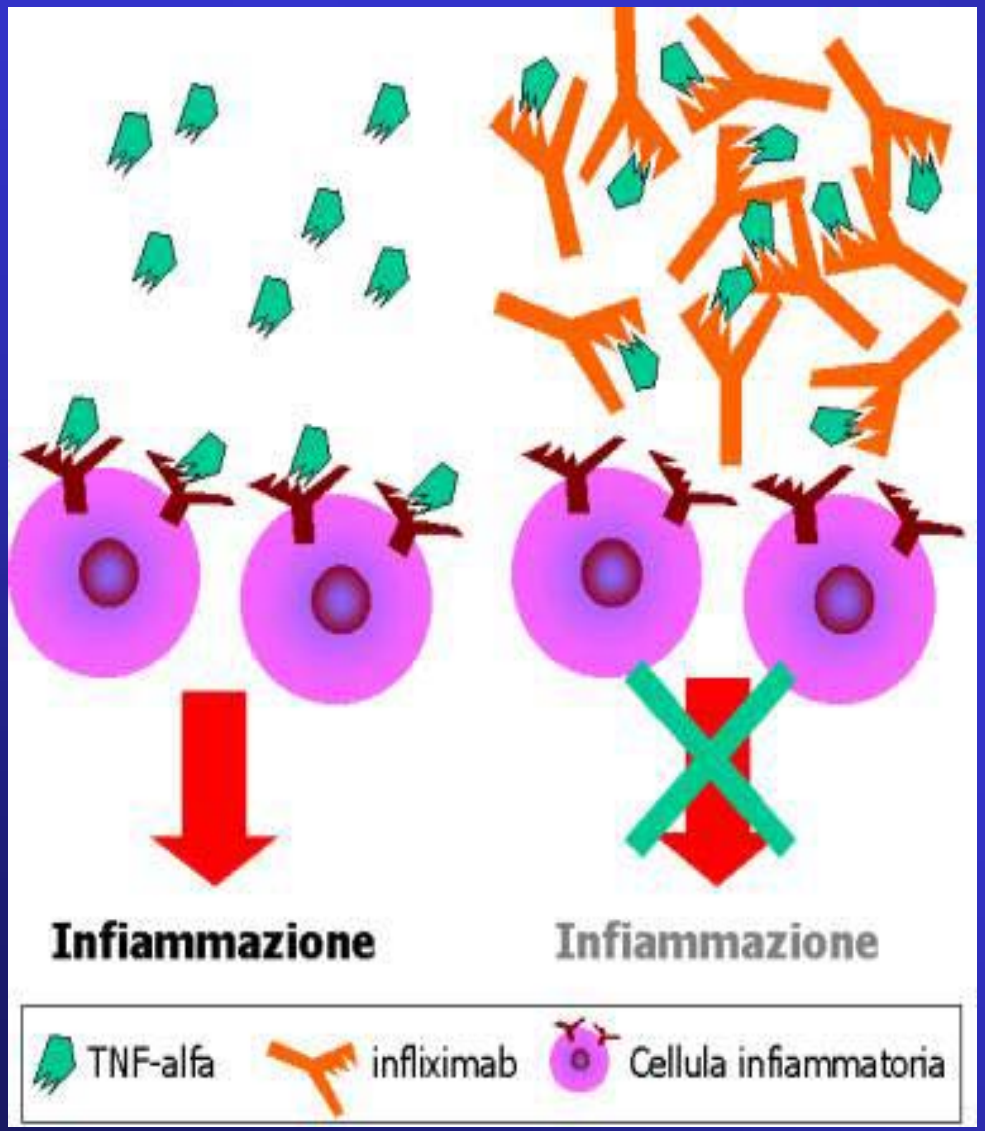
# Monoclonal Antibodies and Pregnancy

1) Bowel Inflammatory Diseases

2) Rheumathoid Arthritis

3) Systemic Lupus Erythematosus

# 1) Bowel Inflammatory Diseases




***Biological therapy improves medical treatment outcomes for refractory patients and raising awareness of the need for maintenance of remission therapy…***

*Aliment Pharmacol Ther 2005; 21: 733–738.*

…more women with BID in the position of being healthy enough to consider pregnancy, it also raises difficult issues about the safety of these medications to the foetus.

# 1) Bowel Inflammatory Diseases

*ntentional infliximab use during pregnancy for induction or maintenance of remission in Crohn's disease*

. MAHADEVAN*, S. KANE, W. J. SANDBORN, R. D. COHEN, K. HANSON, J. P. TERDIMAN* & . G. BINION§

*Aliment Pharmacol Ther 2005; 21: 733–738.*

*" Based on available data, the benefits IFN use in keeping the mother's disease under control may outweigh the unknown risk to the foetus of exposure to drug."*

A summary of published data on infliximab in pregnancy and conception period reported on 151 pregnancy

-19 miscarriages

-18 therapeutic terminations

- 114 live births of whom,one was born 24 wks preterm and died, one had tetralogy of fallot and one had intestinal malrotation

# 1) Bowel Inflammatory Diseases

**Table 1 IBD medications during pregnancy**

| Low risk | Limited data | Not recommended | Contraindicated |
|---|---|---|---|
| Oral mesalamine | Olsalazine | Tetracycline | Methotrexate |
| Topical mesalamine | Azathioprine | Sulfonamides | |
| Sulfasalazine | 6-Mercaptopurine | | |
| Ampicillin | Metronidazole | | |
| Cephlasporins | Ciprofloxacin | | |
| Corticosteroids | Infliximab | | |
| Cyclosporine | Adalimumab | | |
| Loperamide | | | |

**Table 2 IBD medications during nursing**

| Low risk | Limited data | Not recommended | Contraindicated |
|---|---|---|---|
| Oral mesalamine | Olsalazine | Tetracycline | Methotrexate |
| Topical mesalamine | Infliximab | Sulfonamides | Cyclosporine |
| Sulfasalazine | Adalimumab | Azathioprine | |
| Corticosteroids | | 6-Mercaptopurine | |
| | | Loperamide | |
| | | Metronidazole | |
| | | Ciprofloxacin | |

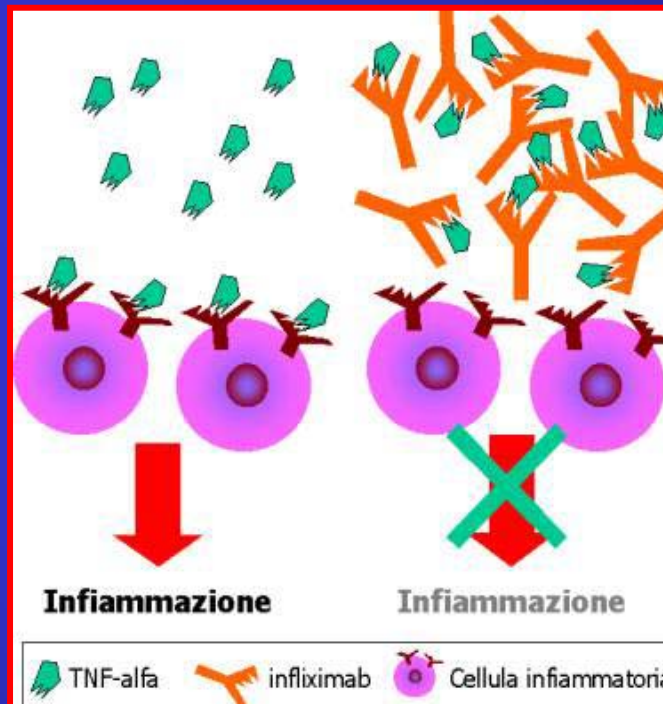
***" Biologic agents are increasingly becoming a mainstay in the treatment regimens of both CD and ulcerative colitis. Unfortunately, little information is available about the short-term and the long-term consequences of treatment with target monoclonal antibodies on the maturing fetus…targeted monoclonal antibodies can be used with caution in pregnant and breastfeeding patient."***

*Stengel, W J of Gastroenterology, 2008*

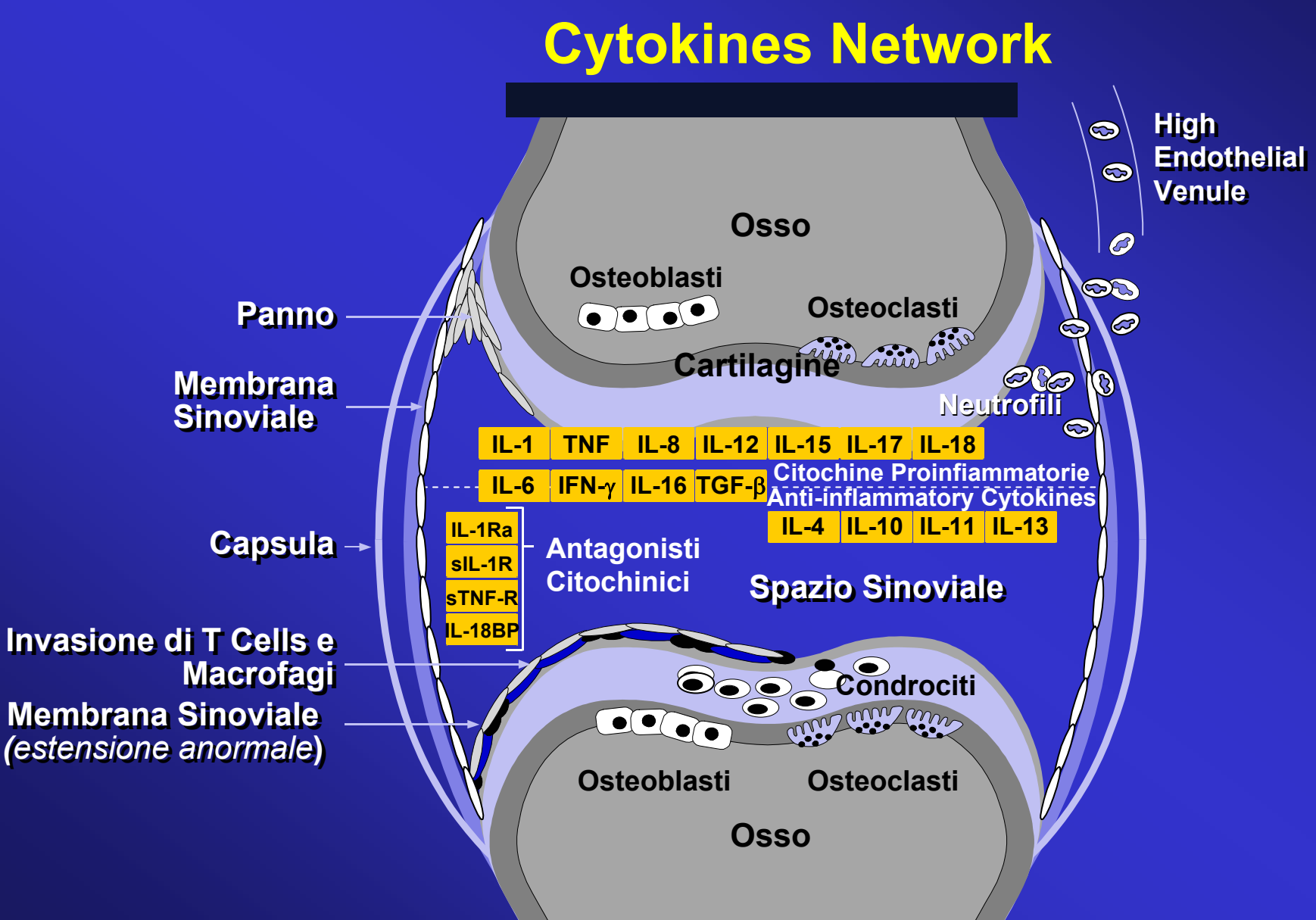
# 1) Bowel Inflammatory Diseases

**The pregnant patients should avoid therapeutic antibody treatments after thirty weeks' gestation and if necessary, the expectant mother can be bridged with steroids to control the disease activity until delivery**

*Stengel, W J of Gastroenterology, 2008*



# 2) Rheumatoid Arthritis



# 2) Rheumatoid Arthritis

***ETANERCEPT*** ***INFLIXIMAB***

*Are indicated for those patients whose RA is inadequately controlled despite treatment for at least 3 months with the standard doses of one the disease modifying antirheumatic drugs*

***Japan College of rheumatology, 2007***

# 2) Rheumatoid Arthritis

***ETANERCEPT, INFLIXIMAB, ANAKINRA***

*These are all categorized as class FDA "B"*

Their prescription before or at conception does not seem to increase the risk of adverse pregnancies or congenital malformation.
At present, however, discontinuation of treatment is racommended when a patient becomes pregnant during therapy. Carefully follow up is mandatory.

LACTATION should be avoided for longer than 6 months from last administration of drugs

*Japan College of rheumatology, 2007*

# 3) Systemic Lupus Erythematosus

- Renal involvement is considered a problem for SLE patient interfering in long term prognosis and survival

- Cyclophosphamide and recently mycophenolate has been considered standard therapy for aggressive lupus nephritis

However,new biologic therapies block selectively the immune mechanisms with the goal of obtaining a more specific anti-inflammatory and immunossoppressive action.

# 3) Systemic Lupus Erythematosus

Case Report:

Severe diffuse proliferative nephritis in pregnant patient with SLE treated with anti-TNF alpha(Etanercept), plasmapheresis and high-dose intravenous gammaglobulin

- no clinical or laboratory flares were observed
- autoantibodies (except anti-Dna) decreased

***" We suggest that a combination of anti-TNF alpha, plasmapheresis and high-dose intravenous gammaglobulin may be safe and effective therapy for pregnant patients suffering severe lupus nephritis."***

*Micheloud D, Lupus 2006*

# Biologic Agents

- ✓ Intravenous immunoglobulins
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# Autologous Hematopoietic Stem Cells

- The reason of this therapy is to try to reset the immune system and achieve self tolerance by eliminating auto-reactive clones
- indications: serious and refractory cases of autoimmune desease
- Complications: fungal infections, septicemia, bleeding, febrile neutropenia,dermatomal zoster, pulmonary oedema, pneumocistis carinii pmeumonia
- Mortality rate is still about 11 to 13 %
- There are still concerns about potential late oncogenicity
- Only in centres with extensive experience

**NO EXPERIENCES IN PREGNANCY**

*Cordeiro, Acta Reumatol Port 2008*

# Conclusions

- *Experience of biologic therapy is still too limited during pregnancy and breastfeeding.*
- *Experts disagree on their use in pregnant women, some stop them and others continue them.*

- *Monoclonal antibodies and other biologic agents can be used with caution in pregnant and breastfeeding.*

*The long term implications on the child's developing immune system are unknown*

# 1) Alloimmune Thrombocytopenia

Due to Human Platelet Antigen incompatibility (HPA-1a most common)

Diagnosis: Newborn
- Unexplained thrombocytopenia (<100K)
- R/O: ITP, DIC, Sepsis, hypoxia

Diagnosis: Pregnant woman
- History of affected child
- Direct relation to such a woman
- Previous child: unexplained thrombocytopenia
- Incidentally found to lack HPA-1a

Diagnosis: Fetal
- Fetal blood
- Fetal DNA from amniocytes, leucocytes, or CVS tissue

# 1) Alloimmune Thrombocytopenia

Due to Human Platelet Antigen incompatibility (HPA-1a most common)

## Losses related to cordoecentesis: Results

| Variable | Case | Control | p |
|---|---|---|---|
| GA | 26.1 | 25.8 | ns |
| Platelet | 5.8 | 32.8 | 0.005 |
| Sib Birth | 16.6 | 31.6 | ns |
| ICH* | 2/5 | 1/43 | 0.02 |

*antenatal

*Paidas AJOG 1995*

# Biologic Agents

- IVIG
- Empiric use should be limited to unusually severe cases characterizzed by:

- - Antierythrocyte alloimmunization with a history of severe fetal hemolysis in spite of conventio treatment with fetal trasfusion

- - History of early onset severe anemia (<20 weeks) when fetal trasfusion is difficult technically

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*" Based on available data, the benefits IFN use in keeping the mother's disease under control may outweigh the unknown risk to the foetus of exposure to drug."*

| uthor | N. | Disease Type | N.infusions | Preg Stage | Preg.outcome |
|---|---|---|---|---|---|
| rinivasan | 1 | CD | 2 | Conception/T1 | Premature 24 wks<br>death at 3 days |
| ames | 1 | CD | 1 | T2 | Live term birth |
| ank | 1 | CD/P | maintenance | Throughout | Live term birth,<br>healthy at 2 yrs |
| urt | 1 | CD | 1 | Conception | Premature at 36 wks<br>healthy at 20 months |
| ichtenstein | 36 | CD | - | any exposure | 11.1% miscarriage<br>(P= 0.53),<br>8.3% neonatal complicati<br>(P=0.78) |
| echant | 1 | P artritis | Maintenance | Conception/T1 | Unknown |
| hakravarty | 2 | RA | Maintenance | Unknown | Live term birth<br>Unknown |
| inder | 1 | RA | Maintenance | Conception/T1 | Miscarriage 6 WKS |
| atz* | 96<br>(100 births) | CD/UC/RA | Various | 7> 3 months prior<br>to conception,<br>53 conception<br>30 T1/ 6 unknown | 68 Live birth<br>preterm death 24 wks<br>full-term tetralogy Fallot.<br>Perinatal sepsis<br>Intestinal malrotation<br>Developmental delay<br>14 miscarriage<br>1 Intrauterine death<br>1 still birth 27 wks<br>18 terapeutic terminations<br>No abnormalities |

* Infliximab safety database

**1) Bowel Inflammatory Diseases**

# 1) Alloimmune Thrombocytopenia

Due to Human Platelet Antigen incompatibility (HPA-1a most common)

## AIT: Natural History

- Usually mild disease
- Platelet count 5-25K
- ICH: 20%
- ICH: 50% occur antenatally

*Paidas update 2007*

# Thrombocytopenia