

DMARDs in Pregnancy and Lactation

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FDA pregnancy categories

Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risk involved in use of the drug in pregnant women clearly outweighs potential benefits

NSAIDs

- ❖ Category B
- ❖ First Trimester miscarriage OR=1.8, 95% CI 1.0-3.2
- ❖ Risk increases with pregnancy duration:
 - Oligohydramnios
 - Renal impairment in mother
 - Premature closure of ductus arteriosus
 - Neonatal bleeding

All NSAIDs move to category D in third trimester because of the concern about premature closure of ductus arteriosus.

- ❖ Considered safe in lactation
- ❖ Minimal quantities excreted in milk
- ❖ ASA use should not exceed 100 mg/d

Corticosteroids

- ❖ Prednisolone <15 mg/d is believed to be safe in Pregnancy.
- ❖ Prednisolone >15 mg/d in 1st trimester increases the risk of neonatal cleft palate from 1/1000 to 1.3-3.3/1000.
- ❖ Prednisolone in any dose increases the incidence of IUGR and preterm delivery.
- ❖ Corticosteroids other than Prednisolone escape placental degradation and reach fetus.
- ❖ Prednisolone is secreted in the milk in $<0.1\%$ of maternal dose.

Hydroxychloroquine

- ❖ Although classified as category C by FDA, and despite transplacental pass and long tissue half life of HCQ there has been no evidence in favor of any congenital abnormality among the neonates who have been exposed to the medication in embryonic and/or fetal period of development.
- ❖ HCQ is safe to be used by lactating women.

Methotrexate

- ❖ Category X
- ❖ First trimester exposure of fetus to MTX carries the risk of Aminopetrin Syndrome: growth deficiency, major bone & CNS & cardiac abnormalities
- ❖ Administration of MTX should be stopped 3-6M before conception.
- ❖ MTX is excreted in breast milk in low dose and is contraindicated during lactation.

Leflunomide

- ❖ Category X
- ❖ Given the long half life of its metabolites, Leflunomide should be stopped 2 years prior to conception.
- ❖ Alternatively, a wash out procedure with cholestyramine should be used until plasma level is <0.02 microgram/ml on 2 measurements 2 weeks apart.

A retrospective study of 64 pregnancies exposed to Leflunomide (61 had cholestyramine wash out) did not find statistically significant congenital abnormalities in the children.

Teratology 2001;63: 106-12

- ❖ Leflunomide is secreted in the milk and contraindicated to be used in breastfeeding.

Azathioprine

- ❖ Category D
- ❖ Although teratogenic in animals, azathioprine have not revealed increased incidence of congenital anomalies in IBD and transplant recipients patients.
- ❖ Complex placental metabolism of azathioprine serves as partial barrier to its metabolites. While 6-thioguanine nucleotides are detectable in fetal blood, 6-methylmercaptopurine is not. *BJOG 2007; 114: 498-501*
- ❖ Breast milk levels of 6-mercaptopurine is very low. Therefore, breast feeding while taking azathioprine seems safe.

Sulfasalazine

- ❖ Category B
- ❖ A meta-analysis of 5-ASA use in IBD pregnant women did not show a significant p-value for stillbirth, miscarriage, preterm delivery, congenital abnormalities, or IUGR. *Reproductive Toxicology 2008; 25: 271-5*
- ❖ Extra folate supplementation is advised for pregnant women on sulfasalazine treatment.
- ❖ Sulfapyridine a metabolite of Sulfasalazine is secreted in the milk. Despite this sulfasalazine is considered safe in lactation.

Cyclosporine

- ❖ Category: C

- ❖ There is maternal risk of HTN and impaired renal function during pregnancy.

- ❖ A meta analysis of 410 pregnancies with prenatal exposure to cyclosporine failed to demonstrate statistically significant increase in malformations, preterm delivery or IUGR relative to controls.

Transplantation 2001, 71: 1051-55

- ❖ Animal studies showed late renal complications in the newborn that were not evident in neonatal state.

Arth Research & Therapy 2006, 8:225

- ❖ Cyclosporine is excreted into human milk with milk-to-maternal serum concentration ratios of less than one (from 0.17 to 0.4). concentrations in milk vary with time of sampling and maternal dose.

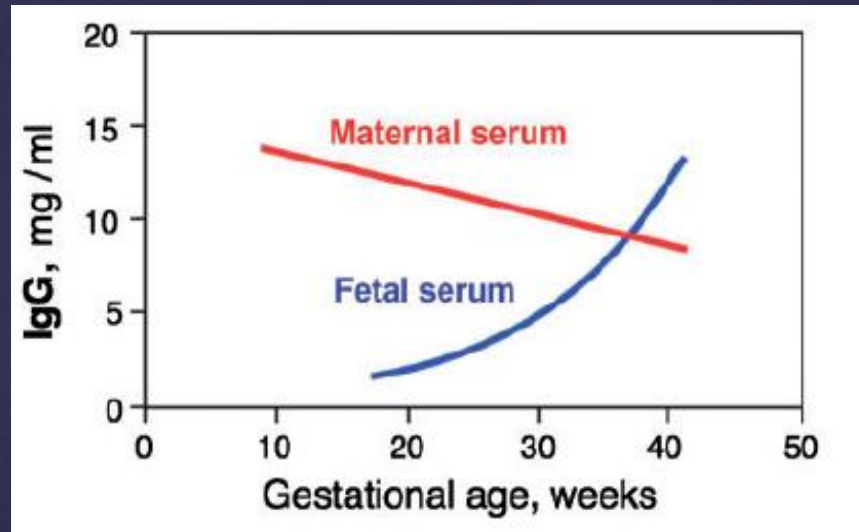
Transplantation 2003; vol. 75 (12), 2144-21-46

Biologics in Pregnancy & Lactation

Anti-TNF

Category B: [animal teratogenicity (-/+), Human safety (?)]

Etanercept
Infliximab
Adalimumab
Golimumab
Certulizumab



- ❖ IgG anti-TNF Abs do not cross placenta in the first trimester .
- ❖ At 13 week of gestation maternal IgG starts to be actively transported to the fetus.
- ❖ Transplacental IgG transport is the most efficient for IgG1 and least efficient for IgG2.

Anti-TNF Studies in Pregnancy

PIANO study (n=426), OTIS registry (n=74), CRIB study (n=31)

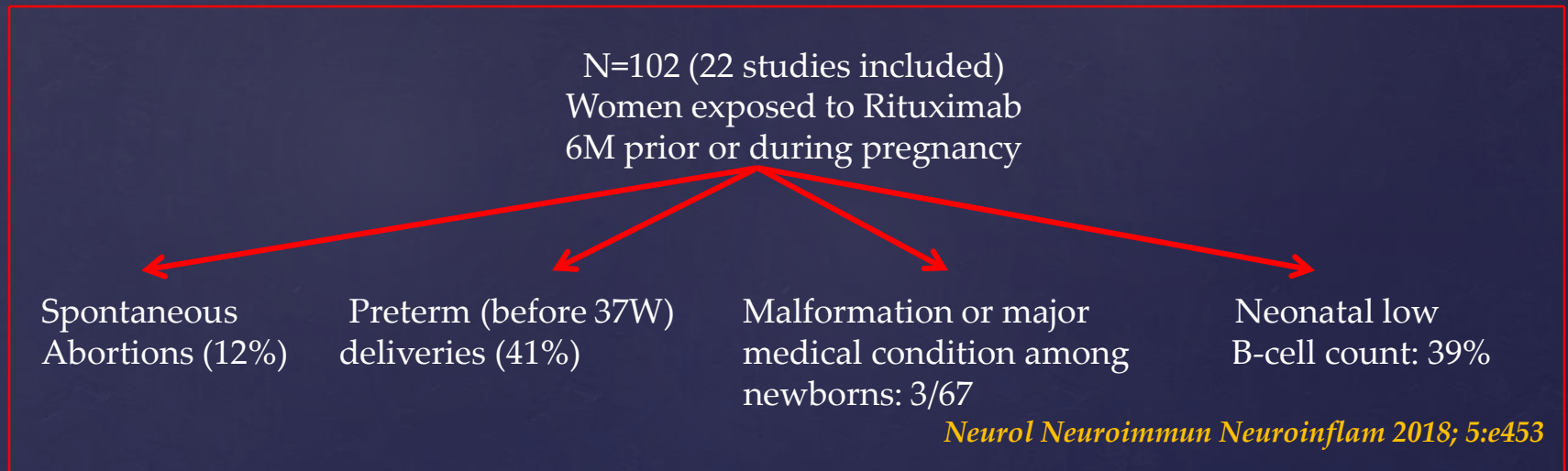
- ❖ Infants exposed to anti-TNF during at least 2nd & 3rd trimesters showed that Adalimumab and Infliximab are detectable up to 12 months after birth while Certulizumab was barely detectable.
- ❖ Anti-TNF Abs were detectable until 6 months after birth.
- ❖ Infants show no apparent major consequences.
- ❖ Given one fatal consequence of BCG vaccinated infant , it is recommended to delay live vaccine immunization of the exposed infants until 12 months or after confirmation of negative drug levels.

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Rituximab

❖Category: C

- ❖Rituximab does not cross placenta until the end of first trimester.
- ❖Effective elimination of Rituximab from maternal blood would require five half lives (19-22 days) or approximately 110 days.

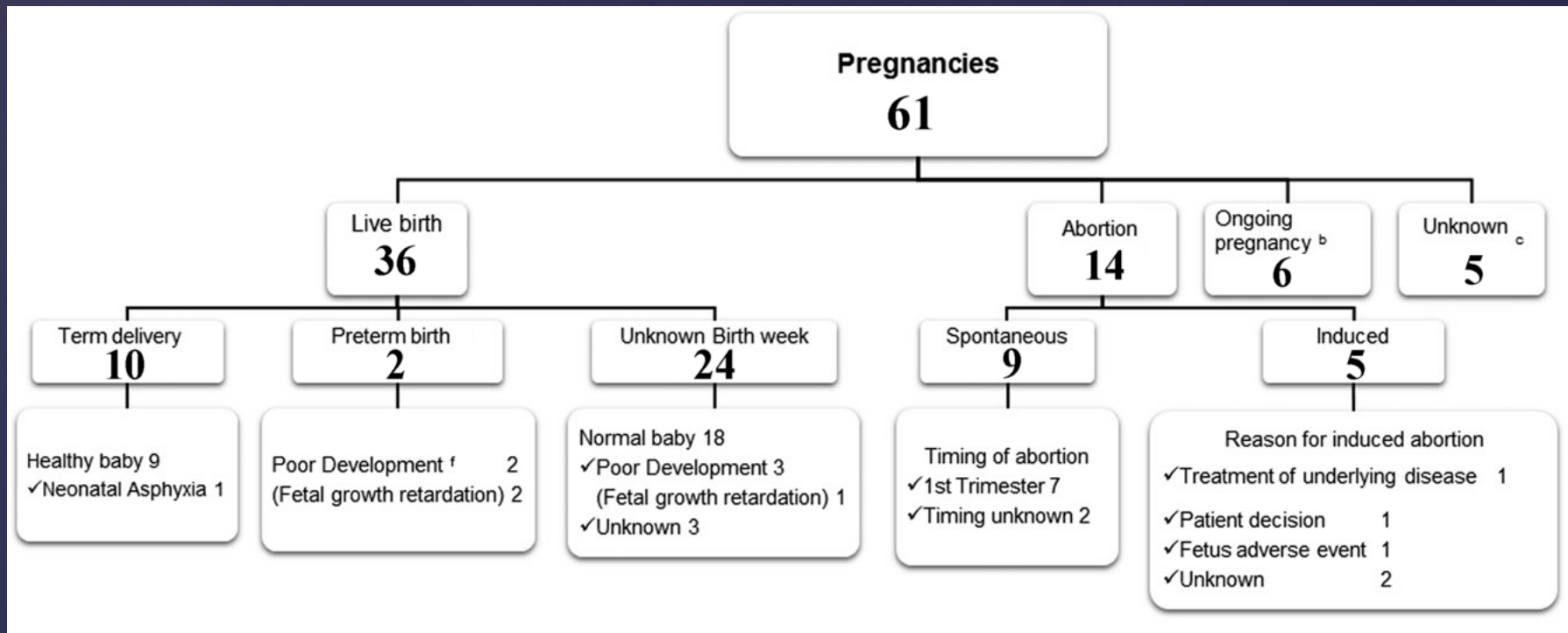


- ❖Neonatal B-cell depletion usually normalizes within 6 months.
- ❖Within first few months of life, the neonates depend on the IgG it received from maternal blood. Therefore, low B-cell count of the neonate is unlikely to cause serious infections.

Clinic Develop Immu 2008, Article ID: 271363

Tocilizumab

Category: C



- ❖ No congenital anomalies noted in 36 newborns.
- ❖ Rates of spontaneous abortions was not more than the expected rate in general pregnancies.

Anakinra

20 pregnancies in 18 mothers with
autoinflammatory syndromes using Anakinra
while pregnant



Median gestational age at delivery 38+4 weeks
Neonatal birth weight 2.02 to 3.94 Kg
APGAR score at birth >9
Two congenital malformations in one baby

Seven babies were breast fed for 3-40 weeks, while their mothers
were using Anakinra . No infection or developmental abnormality
noted.



Thanks