# Treatment of autoimmune disease in pregnancy

Dr. Saremi

- Medication management during pregnancy and lactation is challenging.
- Potential risks to the developing fetus and newborn must be weighed against the benefits of disease control

# Aspirin, Nonsteroidal Anti-inflammatory Medications, and Cyclooxygenase-2 Inhibitors

- **Both NSAIDs and cyclooxygenase-2 (COX-2) inhibitors can potentially interfere with implantation and ovulation**

- **High dose aspirin and NSAIDs are teratogenic in animals,**

- **NSAIDs can cause premature closure of the ductus arteriosus in the third trimester and should be discontinued by 28- 30 weeks' gestation**

- A case report describes constriction of the ductus after local application of **diclofenac gel during week 35 on the shoulder–neck region**
- If used repeatedly during the third trimester, **ductal flow and amniotic fluid volume** should be regularly evaluated by sonography.

- **Antenatal use of NSAIDs, and especially indomethacin, has been associated with NEC in premature infants**

- recent case-control study from the National Birth Defects Prevention Study reported an association between **ibuprofen use and orofacial clefts, spina bifida, and anophthalmy or microphthalmy**

- **Paracetamol is the analgesic and antipyretic of first choice during pregnancy, and can be used in any trimester when indicated.**
- **Intermittent use is advised because of a small risk of wheeze and childhood asthma with prolonged paracetamol use in pregnancy**

- **Avoid regular use during weeks 8-14W of pregnancy due to a small reported risk of cryptorchidism1**
- **analgesia use during pregnancy is not strongly associated with cryptorchidism development in the son, 2**


- **1-** BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part II: analgesics and other drugs used in rheumatology practice- 2016
- 2-Analgesia use during pregnancy and risk of cryptorchidism: a systematic review and meta-analysis.2017

- **Ibuprofen is the analgesic of choice second to paracetamol, and the anti-inflammatory agent of first choice until gestational week 28. Use of diclofenac is also possible.**

- **in the first trimester of pregnancy raise the possibility of a low risk of miscarriage and malformation.**

- **Low-dose therapy with ASA can be used safely without limitations with appropriate indication.**

- **Selective COX-2 inhibitors:**
- FDA pregnancy category: C up to 30 weeks gestation
- FDA pregnancy category: D from 30 weeks gestation

- NSAIDs cross into breast milk at very low concentration; thus these medications are thought to be compatible with nursing.

- Ibuprofen and paracetamol are the analgesics/antiphlogistics of choice during breastfeeding

- Mothers of **jaundiced infants** should avoid those medications metabolized by the liver
- all NSAIDs should be **avoided** in lactating mothers **whose infants have thrombocytopenia**.

# Glucocorticoids

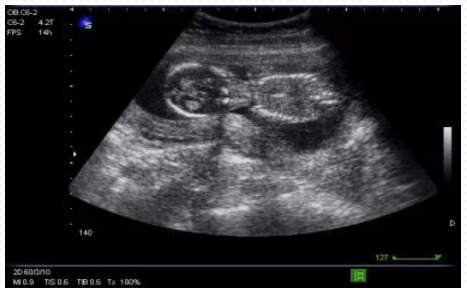
- nonfluorinated glucocorticoids cross the placenta in low concentrations

- fluorinated glucocorticoids such as betamethasone readily cross the placenta

- Glucocorticoid use throughout pregnancy increases risk of
- **pre-term delivery,**
- **small-for-gestational age infants,**
- **maternal hypertension, gestational diabetes.**

# high doses of **glucocorticoids**

- **fetal growth should be observed sonographically.**
- **adrenal insufficiency** in the newborn must be considered and treated if it occurs.
- during weeks 8–11 of pregnancy may warrant an ultrsonographic evaluation of the **fetal face for the detection of clefting of the lip and palate**



- Prednisone and prednisolone cross into breast milk in very low concentrations and can be used in lactating women.
- **When the dose is greater than 20 mg a day**, avoiding breastfeeding within 4 hours of drug administration is recommended.

- **Dexamethasone use during pregnancy has potential adverse effects on embryonic skeletogenesis.** (influence the BMP, FGF, and Wnt signaling pathways)

# Antimalarial Agents

- An antirheumatic therapy can be continued, or even begun during pregnancy.
- Anti-malarials cross **into breast milk** at low concentration, but exposed neonates showed no ocular toxicity
- there are no sufficient grounds for routine ophthalmological examination in the first or second year of life after continuous intrauterine hydroxychloroquine/chloroquine exposure.


# Sulfasalazine

- Sulfasalazine is a poorly absorbed sulfonamide that is metabolized in the intestine to sulfapyridine and 5-aminosalicylic acid (5-ASA)
- sulfasalazine and its metabolites do cross the pla- centa, large case series have not shown evidence for terato-genicity.
- interferes with folic acid absorption,
- **SSZ with folate supplementation (5mg/day) is com-patible throughout pregnancy**

- Sulfasalazine appears in breast milk in significant concentrations.
- A single case of **bloody diarrhea in a breastfed infant has been reported**,
- compatible with nursing.
- Because the active metabolite of sulfasalazine can displace bilirubin, women nursing premature infants, infants with hyperbilirubinemia, or infants deficient in glucose-6-phosphate dehydrogenase **should avoid this medication.**

# methotrexate

- MTX at any dose should be avoided in pregnancy and stopped 3 months in advance of conception

- between 6 and 8 weeks' gestation can lead to **craniofacial and limb malfor- mations** as well as significant developmental delays.

- specific MTX embryopathy, which has been linked to higher dosages, has only rarely been observed after maternal low-dose treatment

- cumulative incidence of spontaneous abortion was 42.5%

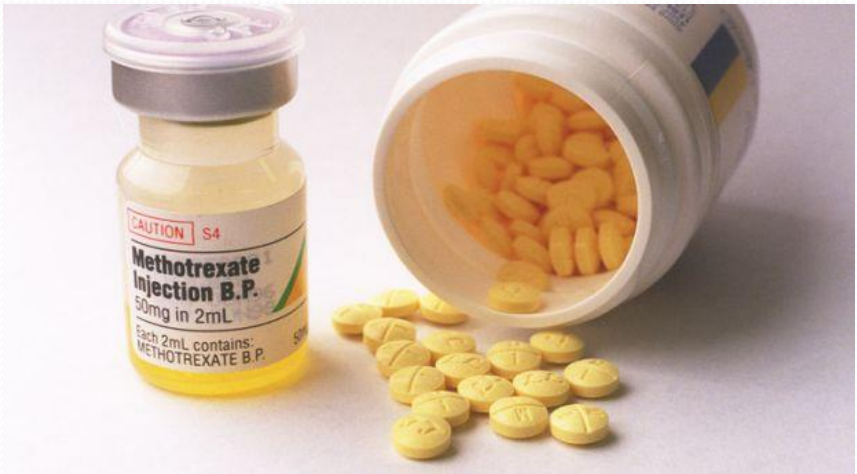
- Methotrexate may cause an increased risk for infertility.
- Low sperm count has been seen in some men using methotrexate

- systematic review from 2009 reported similar results in **101 cases of MTX exposure during the first trimester**.
- Half resulted in live births.
- This study also demonstrated relatively low rates of congenital abnormalities with none thought to represent MTX embryopathy.
- Nineteen pregnancies ended as spontaneous abortions.


- Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). *Clin Exp Rheumatol*. 2009;27(4):678–684

- Low dose not justify a risk-grounded termination of pregnancy .

- treatment should be stopped immediately and a level II ultrasound should be offered to examine fetal development.



# Leflunomide.

- a potent teratogen in rodents
- Skeletal malformations, anophthalmia or microphthalmia and hydrocephalus have been described.
- Up to now, there is no support for the teratogenicity of leflunomide in humans.
- **should not be used during pregnancy**
- **stop LEF 2 years before conception or to treat the patient with a cholestyramine wash-out to remove active metabolites in anticipation of pregnancy.**

- However, given the long half-life, leflunomide should be avoided in lactating women.

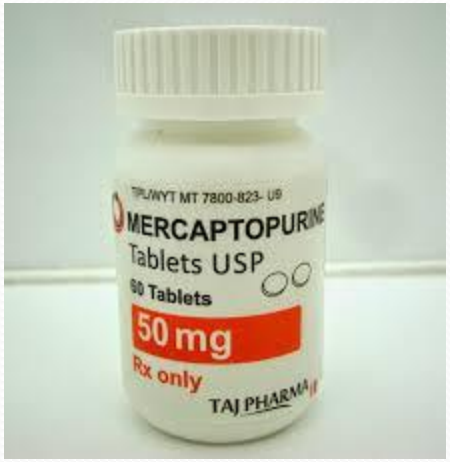
# Azathioprine/6-mercaptopurine

- Azathioprine (AZA) is an antimetabolite which is 80% metabolized to 6-mercaptopurine (6-MP).

- Although azathioprine and 6-mercaptopurine (6-MP) **are category D drugs**, large transplant registries have followed thousands of treated pregnancies and do **not demonstrate an increased rate of congenital anomalies in exposed infants**

- A teratogenic potential in humans has not been recognized. It may be prescribed during pregnancy.
- A detailed ultrasound examination may be offered to confirm normal fetal development

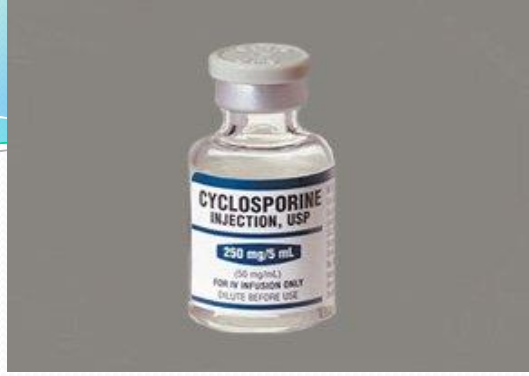
- AZA is compatible throughout pregnancy at 2mg/kg/day
- AZA is compatible with breastfeeding




# cyclospurine

- In a cohort study, in which 39 intrauterine CyA-exposed children were compared with non-exposed children with respect to possible long-term effects, **no differences in intelligence, visual motor abilities and behavior could be determined**

- **A teratogenic potential in humans <u>has not been recognized.</u> It may be prescribed during pregnancy.**




- A detailed ultrasound examination may be offered to confirm normal fetal development

- In 2& 3th trimester Suggested **monitoring of maternal blood pressure, renal function, blood glucose and drug levels.**

- Mothers on CSA should not be discouraged from breastfeeding

# tacrolimus

- It crosses the placenta with in utero exposure being approximately 71% of maternal blood concentra- tions.

- Its pharmacokinetic is altered during pregnancy. Due to decreased albumin level during pregnancy **unbound tacrolimus concentration increases**


- As yet, **no teratogenic potential** has been recognized for humans.
- Systemic use of tacrolimus during pregnancy is acceptable in well- grounded cases

- After tacrolimus exposure in late pregnancy, the **newborn's kidney function and potassium levels should be checked as a precaution.**

# MMF

- MMF is the most recently recognized human teratogen.

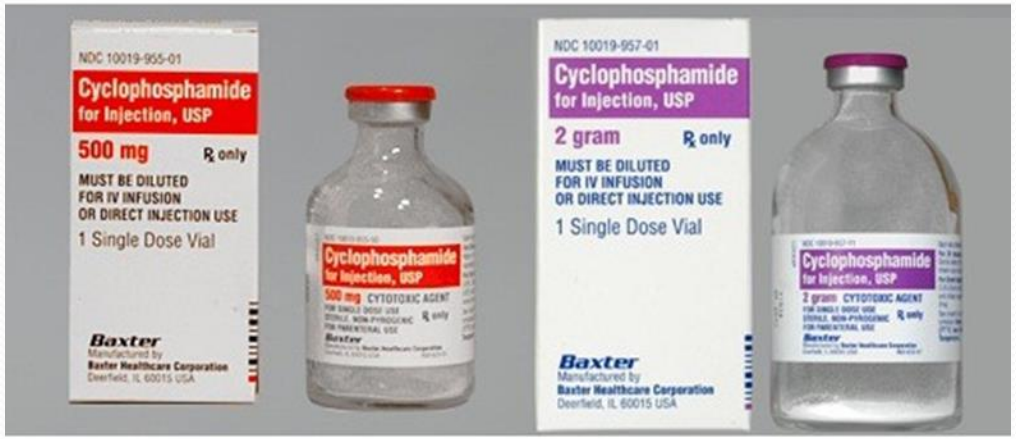
1) **malformations of the ear, in particular, microtia and atresia of the external ear,**
2) **cleft lip, and other malformations such as tracheal-esophageal atresia**
3) **heart defects**

- An accidental exposure during pregnancy does not, however, justify a risk-grounded termination of pregnancy, but a detailed ultrasound examination should be carried out

# cyclophosphamide

- The most frequently described features of this cyclophosphamide embryopa- thy included :
- growth retardation,
- developmental delay,
- microcephaly and major malformations of the distal limbs
- minor anomalies of the **ears, nose, jaw and midface**

- **Maternal treatment with cyclophosphamide later** in pregnancy has not been associated with an increased risk of fetal malformations,
- oligohy- dramnios, premature delivery and neonatal bone marrow suppression are unusually frequent



- **CYC is teratogenic and gonadotoxic, therefore it should only be considered in pregnancy in life-/ organthreatening maternal disease**

# colchicine

- colchicine therapy did not significantly increase the incidence of foetal malformations or miscarriage when taken during pregnancy.
- Colchicine therapy for FMF should not be withheld on this basis during pregnancy.

- When not limited to FMF, colchicine use was associated with a **significantly lower birthweight and gestational age** compared with a control group including healthy women who did not take colchicine

# IVIG

- Clinical experience with immunoglobulins does not suggest a harmful effect on pregnancy or the fetus

- Intact immune globulins cross the placenta increasingly after 30 weeks gestation


- Immune globulin intravenous Pregnancy and Breastfeeding Warnings. Drugs.com

| | *Points to consider for use of antirheumatic drugs in pregnancy** | Grade of recommendat |
|---|---|---|
| 1 | csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare. | B |
| 2 | csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy. | B |
| 3 | Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters. | B |
| 4 | In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered. | D |

# Anti TNF

- Exposure to Anti TNF during the first trimester appears not to be coupled to an increased risk of congenital defects compared with the general population, which is approximately3%, although isolated reports of congenital malformation exist

- (Fuji-kawa, Endo, & Mizokami, 2016

1) **V**ertebral abnormalities,
2) **A**nal atresia,
3) **C**ardiac defect,
4) **T**racheo**e**sophageal,
5) **R**enal,
6) **L**imb abnormalities

**VACTERL**

- **A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database**
- J Rheumatol. 2009 Mar;36(3):635-41

- Female patients with immune mediated diseases treated with anti-TNF-α agents **were at significantly increased risks of preterm birth, spontaneous abortion and low birth weight compared to the general population, but had comparable outcomes with non-users.**

- Outcome of pregnancy and neonatal complications with anti-tumor necrosis factor-α use in females with immune mediated diseases; a systematic review and meta-analysis

- if treatment with biologic agents is required throughout the pregnancy, **use of certolizumab should be considered because it does not cross the placenta in significant amounts**.
- **Etanercept may also be a reasonable alternative because its placental transfer is less than adalimumab or infliximab**

- Update on biologic safety for patients with psoriasis during pregnancy. International Journal of Women's Dermatology. Accepted 16 December 2016

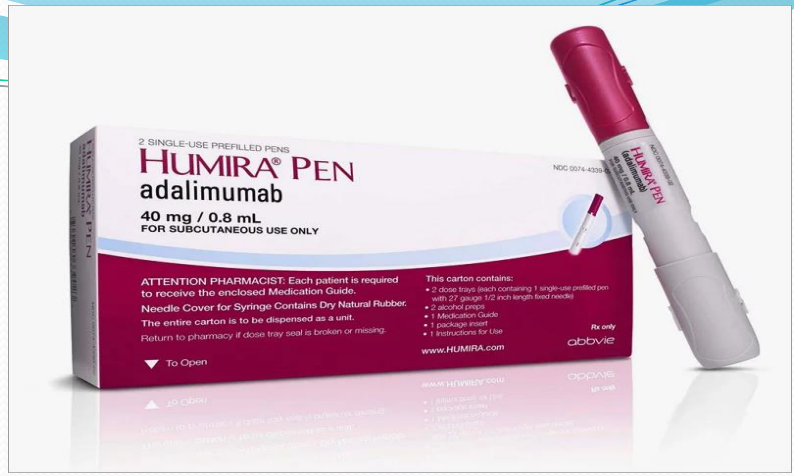
- Only one case of a fatal response to a living vaccine after the **mother was treated with a TNF-inhibitor has been described in the literature.**
- **In 2008 a 28-year-old woman with Crohn's disease was treated with infl iximab throughout her pregnancy.**

- Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. J Crohns Colitis. 2010 Nov;4(5):603-5

- a recently published case report of a 3-month-old preterm infant with chicken pox who fully recovered is reassuring
- His mother received ADA until gestational week 34 and went into labor 2 days later.

- Chicken pox infection in a three months old infant exposed in utero to Adalimumab. J Crohns Colitis. 2013 Apr;7(3):e116-7

# Recommendation




- Adalimumab:
  - ADA does not need to be stopped when planning a pregnancy
  - Discontinuation of therapy is mostly recommended by gestational week 30. A detailed ultrasound examination may be offered to confirm normal fetal development.

  - As a matter of precaution, **children who were exposed to ADA in later pregnancy should not be immunized with a live vaccine before 6 months of life.**

# Etanercept

- There was no evidence of increase in miscarriages or malformations and due to its safety can be continued until **30–32weeks** of pregnancy and if needed throughoutpregnancy

# Infliximab

- IFX does not need to be stopped when planning a preg- nancy.
- However, treatment in the second/third trimester should be reserved for well-grounded indications.
- Discontinuation of therapy is mostly recommended by gestational week 20

- children who were exposed to IFX in the late pregnancy should not be immunized with a live vaccine before the sixth month of life.

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

- Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered.
- Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.

- Women should not be discouraged from breast-feeding on TNFis, but caution is recommended until further information is available

# Rituximab

- chimeric mouse-human IgG-antibody directed against CD20,
- One infant whose mother was treated with rituximab in the first trimester of pregnancy was reported to have a major **congenital anomaly and ventricular septal defect**

- **88 live-born infants whose mothers were treated with rituximab sometime before delivery, and usually before conception**


- RTX should be stopped 6 months before conception.

- Limited evidence has not shown RTX to be teratogenic
- only second-/third-trimester exposure is associated with neonatal B cell depletion.
- Therefore, unintentional RTX exposure early in the first trimester is unlikely to be harmful

- **tocilizumab .**
- should be stopped at least 3 months before conception, but unintentional exposure early in the first trimester is unlikely to be harmful

- **anakinra**

- **abatacept**

# از توجه شما سپاسگزارم