IN THE NAME OF GOD

Managing RA during pregnancy

[illegible]

- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible]

Effect RA on fertility

[illegible] RA [illegible]

- [illegible] RA [illegible]
- [illegible] RA [illegible] RA .
- [illegible] (TTP) [illegible]
- A TTP [illegible] 12 [illegible]
- [illegible]

[illegible] 5%, [illegible] RA [illegible] 25-42%.

Effect RA on fertility

- Several factors are thought to contribute to the impaired fertility in RA patients.
- Some anti-rheumatic drugs have been associated with impaired fertility outcomes.
- Non-steroidal anti-inflammatory drugs (NSAIDs) and high doses of prednisone (>7.5 mg daily) prolong the TTP.
- For NSAIDs, the inhibition of the production of prostaglandins which play a role in ovulation and implantation, is most likely to be responsible.
- The negative effect of prednisone on fertility could be related to a direct effect on the endometrium and ovary and/or suppression of the hypothalamic-pituitary-ovarian axis.

E[illegible] RA [illegible]

- A[illegible]
- [illegible] RA [illegible] HTTP > 1 [illegible] 4% [illegible] (I AS28-CRP > 5.1).
- W[illegible] (I AS28-CRP ≤ 2.4) HTTP > 1 [illegible] 30% [illegible].
- E[illegible] RA [illegible].
- T[illegible] RA [illegible].

[illegible]

- [illegible] Müzik Ödülleri (AMA).
- [illegible] AMA [illegible].
- [illegible] AMA [illegible].
- [illegible] AMA.
- [illegible].

- A prospective cohort from the PARA study in the Netherlands included women who were pregnant or attempting to become pregnant.
- Of 245 patients, 205 (84%) became pregnant with 64 (31%) having a time to pregnancy over 12 months.
- Disease activity as measured by Disease Activity Score in 28 joints (DAS28) was higher among women who did not conceive and those with longer time to pregnancy.
- Other factors associated with longer time to pregnancy included age, nulliparous state, and preconception use of nonsteroidal anti-inflammatory drugs (NSAIDs) and prednisone (>7.5 mg/day).
- Time to pregnancy was not found to be associated with rheumatoid factor (RF) or

Effect RA on fertility

- As a result of impaired fertility rates, RA patients are more likely to receive fertility treatment.
- Assisted reproductive technology (ART) was found safe and effective in one study.
- However, data from the nationwide Danish Health Registries showed a reduced chance of a live birth in women with RA receiving ART compared to a healthy reference group.
- The authors suggested that this was related to an impaired chance of embryo implantation.
- In their study, the use of prednisone before conception increased the odds ratio for live

Effect RA on fertility

- Less is known on beneficial effects of anti-rheumatic drugs on fertility.
- A small retrospective study showed that in RA patients with a wish to conceive, treatment with biologic disease-modifying anti-rheumatic drugs (bDMARD) at the time of conception could shorten the TTP.

Disease course of RA during pregnancy

- Disease activity improves during pregnancy,
- A recent systematic review and meta-analysis by Jethwa et al. found a combined improvement rate of RA during pregnancy of 60%.
- The authors found a combined flare rate post-partum of 46.7%.
- Furthermore, the flare in disease activity has been described after a

Effects of Pregnancy on Rheumatoid Arthritis

- Approximately 50% of pregnant women with RA have low disease activity, and 20% to 40% achieve remission by the third trimester.
- ✓ However, nearly 20% will have worse or moderate-to-high disease activity during pregnancy that may require further therapeutic intervention.
- ✓ Disease activity itself is a clinical feature associated with the disease course of RA during pregnancy.
- ✓ RA patients in low disease activity in the first trimester are likely to have low disease activity or remission in the last trimester.

Equipment and Personnel Requirements

- Radio frequency (RF) and audio-video (AV) equipment
- All RF and AV equipment must be tested and approved by the Event Technical Manager
- Personnel must be qualified and trained in the use of the equipment.
- All equipment must be set up and operated by authorized personnel.

- Data on pregnancy outcomes in RA patients are well documented and reported in previous literature .
- Compared to the general population, pregnancy outcomes in RA patients are slightly less favorable and related to active disease.
- In patients with well-regulated disease pregnancy outcomes are comparable to the general population.

Pregnancy outcomes

Compared with women without RA, women with RA were more likely to develop :

- Pre-eclampsia/eclampsia.
- Gestational diabetes.
- Preterm premature rupture of membranes(PPROM),Placental abruption and placenta previa.
- Deliver by caesarean section. risk of miscarriages ,SGA, IUGR, lower birth weight ,preterm birth be increased .
- Postpartum, RA-complicated pregnancies were associated with wound complications and thromboembolisms.

OFFSPRI NG

- Of f s pring o f RA pat ient s do no t h av e an increas ed ris k o n mayo r co ngenit al mal f o rmat io ns .
- Lo ng-t erm f o l l o w-up o f o f f s pring o f RA pat ient s rev eal ed no dif f erences in ant h ro po met ric meas urement s co mpared t o ch il dren b o rn t o h eal t h y mo t h ers .

Managing RA during pregnancy

- Treating RA before and during pregnancy can be challenging since some drugs are considered teratogenic and active disease is associated with adverse fertility and pregnancy outcomes.

- Disease activity improves during pregnancy, but less than previously anticipated.

- A significant number of patients has active disease and the use of anti-rheumatic drugs is still required.

Ho w is rh eumat o id art h rit is (RA) t reat ed during pregnancy?

- No ne o f t h e medicat io ns us ed in t h e t reat ment o f rh eumat o id art h rit is (RA) is ab s o l ut el y s af e during pregnancy.
- Hence, t h e decis io n t o us e medicat io ns s h o ul d b e made af t er caref ul as s es s ment o f t h e ris ks and b enef it s in co ns ul t at io n wit h t h e pat ient .
- Th e ph ys ician pro v iding o b s t et ric care needs t o wo rk cl o s el y wit h t h e pat ient 's rh eumat o l o gis t , es pecial l y if t h e pat ient is t aking dis eas e-

What is included in preconception counseling of women with rheumatoid arthritis (RA)?

- It is important to counsel women of childbearing age about the teratogenicity and adverse effects of the medications used to treat rheumatoid arthritis (RA) before starting therapy.
- These patients may need a reminder about the importance of using contraception during therapy with disease-modifying antirheumatic drugs (DMARDs), especially methotrexate, leflunomide, and cyclophosphamide.
- Educate patients that because of a prolonged half-life, some of these medications may need to be discontinued several months before conception is planned.

Medication during pregnancy

- Guidelines for the use of antirheumatic drugs during pregnancy have been released by the European League Against Rheumatism (EULAR) and jointly by the British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR).

Conventional disease modifying anti-rheumatic drugs (cDMARD), NSAIDs

- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be stopped at the beginning of a menstrual cycle when conception is planned, because these agents have been shown in animal studies to interfere with blastocyst implantation.
- Most traditional NSAIDs are considered category B medications but should be used with caution in pregnancy.
- Stopping NSAID therapy before 32 weeks' gestational age is prudent for potentially avoiding adverse effects to the fetus. Short-acting NSAIDs(eg, ibuprofen, indomethacin, diclofenac) are preferred over long-acting agents.

Conventional disease modifying anti-rheumatic drugs (cDMARD), NSAIDs

- Possible effects on the mother include:
  - Prolonged gestation and labor.
  - Increased peripartum blood loss,
  - Increased anemia.
- The potential adverse effects to the fetus include:
  - Impaired fetal renal function oligohydramnios and increased cutaneous and intracranial bleeding.
  - Monitoring for oligohydramnios should be considered if the pregnant patient is on prolonged NSAID therapy.

The EULAR guidelines make the following recommendations regarding the use of NSAIDS

- Non-selective (classic) NSAIDS: Can be continued during the first and second trimesters based on current evidence indicating no increased rate of congenital malformations.

- Selective COX-2 inhibitors: Should be avoided in pregnancy due to insufficient evidence of fetal safety

Corticosteroids

- Corticosteroids may increase the maternal risk of hypertension, edema, gestational diabetes, osteoporosis, premature rupture of membranes, and small-for-gestational-age babies, IUGR and PROM
- One meta-analysis found a 3.5-fold increase in the risk of cleft palate in fetuses with first-trimester exposure to corticosteroids.
- Prednisone is largely metabolized by the placenta.
- The use and period of prednisone before and during pregnancy should be limited however.

Corticosteroids

- Therefore, if steroid treatment is desired for the mother, hydrocortisone, cortisone,or prednisone shoul d be chosen.

- Dexamethasone and betamethasone cross the placenta with similar maternal and fetal concentrations; thus, they are the treatment of choice for fetal respiratory distress.

Corticosteroids

- The lowest possible steroid dose needed to control disease activity should be used in pregnancy.

- Stress doses of steroids should be used during labor and delivery if the mother received steroids (even low-dose) for more than 2-3 weeks during pregnancy, and the neonate should be monitored for evidence of adrenal insufficiency and infection.

EULAR and BSR-BHPR guidelines

- The EULAR guidelines make the following recommendations for use of corticosteroids :Prednisone: Can be continued at the lowest effective dose throughout pregnancy, based on current evidence indicating no increased rate of congenital malformations

- BSR-BHPR guidelines: find prednisone use acceptable in each trimester of pregnancy. The guidelines notes that methylprednisolone has rates of placental transfer similar to prednisolone with equivalent anti-inflammatory effects at 80% of prednisolone dose. Therefore its use is expected to be compatible with pregnancy.

Is methotrexate (MTX) safe for pregnant women with rheumatoid arthritis (RA)?

- Methotrexate (MTX), a folic acid antagonist, is contraindicated in pregnancy (category X).

- Because it is an abortifacient and has teratogenic effects, such as causing the development of craniofacial abnormalities, limb defects, and such CNS defects as anencephaly, hydrocephaly, and meningomyelopathy, especially with first-trimester exposure.

EULAR and BSR-BHPR guidelines

- Both the EULAR and BSR-BHPR guidelines recommend MTX at any dose should be avoided in pregnancy and stopped 3 months in advance of conception.
- BSR-BHPR guidelines further recommend that women treated with low-dose MTX within 3 months of conception receive folic acid supplementation prior to and throughout pregnancy.
- In the case of accidental pregnancy in a woman on low-dose MTX, the drug should be stopped immediately, folic acid supplementation continued, and a careful evaluation of fetal risk carried out by local experts.

EULAR and BSR-BHPR guidelines

- A 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.

Leflunomide

- Its half-life is 14-15 days, but the active metabolite undergoes extensive enterohepatic circulation; thus, the drug takes up to 2 years to be undetectable in plasma.
- Consequently, discontinuation of the drug before conception is insufficient.
- The drug needs to be eliminated with administration of cholestyramine (8 g tid for 11 d).
- Plasma levels of less than 0.02 mg/L should be verified with 2 separate tests at least 2 weeks apart.
- If unacceptably high levels persist, additional cholestyramine may be need .

EULAR and BSR-BHPR guidelines

- Both the EULAR and BSR-BHPR guidelines recommend avoiding leflunomide in pregnancy and completing a cholestyramine washout procedure prior to conception.
- BSR-BHPR guidelines further recommend that if accidental conception occurs during leflunomide therapy, the drug should be stopped immediately and cholestyramine washout given until plasma levels are undetectable.

Sulfasalazine

- Sulfasalazine (SSZ), a dihydrofolate reductase inhibitor, is a category B medication; it does not increase fetal morbidity or mortality and is considered safe in pregnancy.
- Both EULAR and BSR-BHPR guidelines support continuation of sulfasalazine wtith folic acid supplementation throughout pregnancy, based on current evidence indicating no increased rate of congenital malformations.

Azathioprine

- Azathioprine (AZA), although a category D medication, can be used if the benefits outweigh the risks.

- AZA crosses the placenta, but the fetal liver lacks the enzyme inosinate pyrophosphorylase, which converts AZA to its active metabolite, 6-mercaptopurine; thus, the fetus is protected from the agent's teratogenic effects.

EULAR and BSR-BHPR guidelines

- Both EULAR and BSR-BHPR guidelines support continuation of AZA throughout pregnancy in doses < 2 mg/kg/day, based on current evidence indicating no increased rate of congenital malformations.

Hydroxychloroquine

- Previous reports of fetal toxicity with this agent were based on the effects of chloroquine, which has 2.5 times the amount of tissue deposition as HCQ.

- No fetal toxicity is associated with HCQ at the dosage used for RA and connective-tissue disease (6.5 mg/kg body weight).

- Several studies and case series have provided further evidence that no fetal toxicity is associated with HCQ therapy in mothers.

EULAR and BSR-BHPR guidelines

- BSR-BHPR guidelines find HCQ the antimalarial of choice in women with rheumatic disease who are planning a pregnancy and recommend continuing use during pregnancy.

- EULAR guidelines also support use throughout pregnancy, based on current evidence indicating no increased rate of congenital malformations

Tumor necrosis factor–alpha antagonists

- Medications in the anti–tumor necrosis factor (TNF)-alpha class (eg, etanercept, adalimumab, infliximab, golimumab, and certolizumab) are commonly used in the treatment of RA.

- These agents have been labeled as class B medications; animal studies have shown no harm to the fetus.

The EULAR guidelines make the following recommendations for use of anti-TNF medications

- Infliximab/adalimumab: Can be continued up to 20 weeks gestation; if indicated, it can be used throughout pregnancy, based on current evidence indicating no increased rate of congenital malformations

- Golimumab: Because of limited evidence, alternative medications should be considered for treatment throughout pregnancy.

- Etanercept: Can be continued up to 30–32 weeks of gestation; if indicated, it can be used throughout pregnancy, based on current evidence indicating no increased rate of congenital malformations

- Certolizumab: Can be used throughout pregnancy, based on current evidence indicating no increased rate of congenital malformations

BSR-BHPR guidelines include the following recommendations

- Infliximab (IFX) may be continued until 16 weeks and etanercept (ETA) and adalimumab (ADA) may be continued until the end of the second trimester
- To ensure low/no levels of drug in cord blood at delivery, ETA and ADA should be avoided in the third trimester and IFX stopped at 16 weeks.
- If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 6 months of age.
- Certolizumab is compatible with all three trimesters of pregnancy and has less placental transfer than other TNF inhibitors (TNFs)
- Golimumab is unlikely to be harmful in the first trimester .

Disease activity after stopping anti-TNF during pregnancy

- There is only limited data available on the effect of stopping anti-TNF treatment on disease course in pregnant patients.

- Most literature suggests that stopping TNF inhibitors just before or during a pregnancy results in a flare during pregnancy or in the peri- and postpartum period.

- Förger et al. showed that in patients with inactive disease, discontinuing TNF inhibitors before the 20th week of gestation did not result in active disease later in pregnancy.

Rituximab

- It is a pregnancy category C medication and should be stopped 12 months prior to attempting conception.

- Case reports have also shown that rituximab therapy results in detectable levels of the drug in cord blood and results in B-cell depletion in the mother and the neonate.

Rituximab

- Recovery of B-cell levels in the neonate has been reported to occur at age 3-4 months and does not appear to impair antibody formation in response to immunizations.
- The dosing of rituximab in case reports was 375 mg/m^2 for 1-6 cycles.
- Mothers and newborns exposed to rituximab during second and third trimester should be monitored for the risk of infections, since neutropenia and B-cell depletion have been described in newborns.

EULAR and BSR-BHPR guidelines

- The EULAR guidelilnes recommend: use in exceptional cases early in gestation; use at later stages of pregnancy increase risk of B cell depletion and other cytopenias in the neonate.

- BSR-BHPR guidelines recommend :stopping rituximab 6 months before conception

Anakinra

- Anakinra is a pregnancy category B medication. No adverse effects have been reported in rats and rabbits receiving up to 100 times the recommended human dose.
- No data are available to indicate whether anakinra is excreted in human milk.
- Very little information is available on its effects in pregnancy.
- Less than 20 cases have been reported in the literature. The largest series evaluated 9 births to women with cryopyrin-associated periodic syndromes and anakinra exposure.
- No other birth defects or premature delivery were noted
- Citing an insufficient documentation of fetal safety.

EULAR and BSR-BHPR guidelines

- EULAR recommends use of anakinra before and during pregnancy when there are no other well-studied options available for treatment.

- BSR-BHPR guidelines note there is limited evidence on which to base a recommendation for use of anakinra in pregnancy, but unintentional exposure in the first trimester is unlikely to be harmful.

Abatacept

- Abatacept is considered a pregnancy risk factor C and should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

- Attempts to conceive should occur 14 weeks after the last abatacept dose, which would correlate with five half-lives of abatacept.

EULAR and BSR-BHPR guidelines

- Both EULAR and BSR-BHPR guidelines recommend avoiding treatment with abatacept during pregnancy, due to the lack of data on fetal safety.

Tocilizumab

- Similarly, there is insufficient information with regard to tocilizumab use and pregnancy. It is categorized as a risk factor C.
- -A total of 33 pregnancies with tocilizumab exposure have been reported with eleven term deliveries. In seven, a spontaneous abortion occurred with five of those also receiving MTX. An additional 13 had an elective abortion, while the outcome in two was unknown. There was one death that occurred at 3 days due to acute respiratory distress syndrome following intrapartum hemorrhage due to placenta previa.

JAK inhibitors

- Three Janus kinase (JAK) inhibitors (baricitinib, tofacitinib, and upadacitinib) are approved in the United States for the treatment of patients with RA.

- Pregnant and lactating women should avoid use of JAK inhibitors.

JAK inhibitors

- ✓ Baricitinib: Data in pregnant women are insufficient to inform a drug-associated risk for major birth defects or miscarriage.
- ✓ Tofacitinib: No adequate and well-controlled studies of tofacitinib therapy in pregnant women have been published, but in the tofacitinib clinical development programs, birth defects and miscarriages were reported.

Upadacitinib

- Limited human data on use in pregnant women are not sufficient to evaluate a drug-associated risk for major birth defects or miscarriage.
- Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.
- Females of reproductive potential should use effective contraception during treatment and for 4 weeks after the final dose.

Vaccination after exposition to anti-TNF in utero

- Infants who are exposed in the 2nd or 3rd trimester of pregnancy to anti-TNF treatment should not receive live attenuated vaccines in their first 6 months of life .
- Infants who are exposed to anti-TNF treatment before the 22nd week of gestation can get vaccinated, including live vaccines, conform the standard vaccine protocols .
- Vaccination appears to be effective in infants exposed to TNF inhibitors in utero.

Anti-rheumatic drugs and their compatibility during pregnancy

Medication	Pregnancy
Hydroxychloroquine	No increased risk on congenital malformations, may be used throughout pregnancy
Sulfasalazine	No increased risk on congenital malformations, may be used throughout pregnancy up to 2000 mg daily with folate supplementation
Glucocorticoids	No increased risk on congenital malformations, may be used throughout pregnancy at lowest possible dose. Prednisone use is associated with preterm delivery. and high dose prednisone (>7.5mg daily dose) use is associated with a prolonged time to pregnancy.
Methotrexate	Proven teratogenic. Not recommended for use during pregnancy. Must be stopped 3 months before planned pregnancy
Leflunomide	May be teratogenic, insufficient data available. Not recommended for use during pregnancy. Washout period with Cholestyramine is recommended before pregnancy

Anti-rheumatic drugs and their compatibility during pregnancy

Medication	Pregnancy
NSAIDs	No increased risk on congenital malformations. Should be stopped in third trimester of pregnancy
Certolizumab	No increased risk on congenital malformations, may be used throughout pregnancy
Infliximab	No increased risk on congenital malformations. Advised to be stopped before 20th week of pregnancy
Adalimumab	No increased risk on congenital malformations. Advised to be stopped before 20th week of pregnancy

Anti-rheumatic drugs and their compatibility during pregnancy

Medication	Pregnancy
Etanercept	No increased risk on congenital malformations. Advised to be stopped before 32nd week of pregnancy
Golimumab	No increased risk on congenital malformations, insufficient data available. Not recommended for use during pregnancy
Other biologicals (Rituximab, Anakinra, Ustekinumab, Tocilizumab)	No increased risk on congenital malformations (Rituximab, Anakinra, Ustekinumab), insufficient data available. Not recommended for use during pregnancy

CONCULUSION

- Rheumatoid Arthritis (RA) is common in the reproductive age.
- Women with RA have an impaired fertility related to the use of certain medication and active disease.
- RA usually improves during pregnancy,
- However almost half of the patients still have active disease in third trimester.
- Pregnancy outcomes are slightly less favorable, especially in women with high disease activity.

CONCULUSION

- Tight disease control during pregnancy and in the postpartum period for patients with active disease is advised to limit complications.
- However a substantial percentage of women with RA has active disease during pregnancy and therapeutic interventions are required.
- Fortunately, accumulating evidence shows the safety of many medications including TNF inhibitors before and during pregnancy.

References

- Yvette Meissner ,etal,European Network of Pregnancy Registers in Rheumatology (EuNeP)—an overview of procedures and data collection
- , *Arthritis Research & Therapy* volume 21, Article number: 241 (2019)
- Rubbert-Roth A, Goupille P, Moosavi S, Hou A. First experiences with pregnancies in RA patients receiving tocilizumab therapy. Arthritis Rheumatol. 2010;62(Suppl 10).
- Mahadevan U, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clin Gastroenterol Hepatol. 2013.
- Katherine K ,etal,Management of rheumatoid arthritis during pregnancy: challenges and solutions, Rheumatol. 2016.
- Katherine K ,etal,Rheumatoid Arthritis and Pregnancy Medscape Apr 07, 2020
- Hissah AljaryPregnancy outcomes in women with rheumatoid arthritis: a retrospective population-based cohort study, The Journal of Maternal-Fetal & Neonatal Medicine Volume 33, 2020 ,
- T.W.SmeeleRpregnancy and childbirth in patients with Rheumatoid Arthriti semaarthritis 2019.