Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

Rheumatoid Arthritis and Fertile Female: A Comprehensive Review of Management During Pre-Conception, Gestation and Lactation.

Dr. Syam Nath S H[1], Dr Vishnu Senthil[2], Dr. Manish Khanna[3], Dr. Venkatesh Kumar S[4], Dr. Ashwin Roby[5], Dr.Habby T Jacob[6]

[1]Assistant Professor, Department of Orthopaedics, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Thiruvananthapuram, 695607, Kerala, India.

[2]Assistant Professor, Department of Orthopaedics, Government Royapettah Hospital, Chennai 14, Tamil Nadu, India.

[3]Department of Orthopaedics, Dean Academics, Dr KNS MIMS, Barabanki, Lucknow, Uttar Pradesh, India.

[4*]Assistant Professor, Department of Orthopaedics, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur - 621 113. Tamilnadu, India

[5]Assistant Professor, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Thiruvananthapuram

[6]Senior Resident, Sree Gokulam Medical College and Research Foundation, Venjaramoodu, Thiruvananthapuram

*Corresponding author: Dr Venkatesh Kumar.S, Assistant Professor, Department of Orthopaedics, Dhanalakshmi Srinivasan Medical College And Hospital, Siruvachur, Perambalur - 621 113. Tamilnadu, India

(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS

Rheumatoid, pregnancy, lactation, postpartum, feeding, biologics, DMARDs

ABSTRACT:

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder that causes significant physical disability, and it affects women three times more commonly than men. It is often seen in their childbearing years. Data on the annual incidence of the disease also suggests a very high percentage in the child-bearing age group. So understanding their problems and finding a solution will be critical for a health care professional taking care of them. Decisions about parenthood also become challenging, as they are affected by perceptions of their disease state, health care needs, and complex pharmacological treatments. There is undoubtedly a clear need to support these vulnerable women through this important period of their lives. The management of RA has revolutionized in recent years. The availability of novel therapies, such as biological agents and treatment paradigms, has substantially improved treatment outcomes for patients with RA. Unfortunately, data on the safety of many of these medications is limited, and many may be contraindicated during pregnancy and breastfeeding. To stabilize the disease before conception and to modify the drug regime, coordinated and careful planning is needed. Recent studies showed that only 20–40% of patients with RA achieve remission by the third trimester. Although 50% may be considered to have low disease activity, nearly 20% will have worse or moderate-to-high disease activity during pregnancy and may require further therapeutic intervention. Many women commonly report postpartum relapses, making them unable to properly care for themselves and their children. A lot of women can find it difficult to access information that could help them plan for pregnancy, lactation, and early parenting concerning their chronic conditions. The accessibility and variety of the pharmacotherapeutic agents support disease control optimization before conception and contribute to the success of the female raising of children, but they should be provided with a detailed understanding of their risks and safety in the setting of pregnancy and breastfeeding. It is a hard nut to crack for healthcare providers to use individualized treatment plans not only for treating active disease but also for maintaining disease

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

remission during the period of preconception, pregnancy, and postpartum. Through the review, we are trying to identify the various issues that rheumatologists face in taking care of women and men in the reproductive age group who wish to start a family. In addition, it explores evidence-based approaches and emphasizes the safe use of disease-modifying antirheumatic drugs and biologics in the care of pregnant and lactating women with RA.

1 Introduction

Rheumatoid arthritis is a chronic, systemic, inflammatory, autoimmune disorder, that affects mainly the synovial joints and musculoskeletal structure. Commonly it presents as swelling and multiple joint pain and can lead to destruction and deformity of the joints resulting in chronic pain and disability along with damaging other systems of the body; especially if the disease is not controlled properly[1–3].

RA affects about 0.5-1.0% of the population worldwide; varying on the geography. Women are more likely to have the disease than men (F: M - 2:1 to 3:1)[4, 5]. For a woman in her reproductive age, the most commonly affected chronic disease will be Rheumatoid arthritis. The disease itself and the medications make it more difficult for them to become and stay pregnant also[6–8]. It is not uncommon for a woman with RA to become pregnant, but the treatment is challenging due to the limited safety data of the commonly available anti-rheumatoid drugs.

Even though there are many safety guidelines available, the treating physician faces different challenges in managing such patients as treatment needs to be individualised in different situations.

For example, a Rheumatoid female with reproductive potential can come to the clinic in different situations like:-

1. When she is not planning for a child now.
2. When she wants to get pregnant.
3. When she comes with a positive pregnancy test.
4. When she got a flare during pregnancy. Or
5. When she is considering breastfeeding after delivery.

Or a Rheumatoid male who is planning for a child, all require different approaches, management strategies and counselling. It is a difficult task to find individualised treatment plans for treating active disease and maintaining remission during the preconception phase, pregnancy, and postpartum.

Therefore, it is important to plan and adjust the treatment before conceiving. For those who can and want to have children, their plans and preferences should be discussed. Those who do not want to get pregnant now but may want to later should be informed about how the drugs they take for RA may affect their fertility or pregnancy[9]. A male patient who wishes to start family planning also needs appropriate counselling and guidance because of potential problems that can arise in fertility and conception.

Managing a patient with rheumatoid arthritis while she wishes to conceive, pregnant, or during lactation will need a different and comprehensive approach (Fig1). Obstetricians and Rheumatologists/ Physicians/ Orthopaedicians have to work as a team and have to explain and educate the patient regarding the potential fertility problems, disease activity during the pregnancy period, outcomes of pregnancy and the postpartum period. And regarding the medications to use in the preconception period, during pregnancy and lactation. The goal is to achieve good control of the disease with minimum risk due to medications.

By this review, we are trying to solve various challenges faced by rheumatologists, physicians, orthopaedicians and obstetricians providing care to men and women (during preconception, pregnancy and while lactating) with rheumatoid arthritis in the reproductive age group wishing to start a family. Also, try to find out the latest evidence-based solutions focusing on the safe use of disease-modifying antirheumatic drugs and biological response modifiers to assist in the care of pregnant and lactating women with RA and to come up with a safe strategy for managing them.

2 Effect of pregnancy on the disease activity

Since Dr. Hench's[11] publication in 1938, many studies have confirmed his findings about the

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

spontaneous improvement of signs and symptoms of inflammatory arthritis (especially RA) during pregnancy and an increased risk of flaring of symptoms postpartum[12–17]. However, these data need to be considered with caution as they were mostly small retrospective analyses without any validated clinical scores. Many newer studies using validated clinical scores came up later in contradiction to these old thoughts, stating lesser number of pregnant patients with RA are getting spontaneous improvement in signs and symptoms during pregnancy. Moreover, a large majority develop flare symptoms in the postpartum period[18–21].

One reason why newer studies show lower improvement rates of RA than older studies is that RA treatments have improved a lot in the past years and so if RA is well-controlled before getting pregnant, there is less chance for pregnancy to improve it. Apart from that newer studies used more accurate and objective ways to measure RA activity and avoided recall bias.

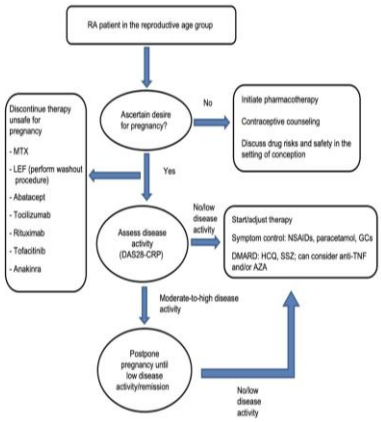

Fig. 1 Approach to management of patients with RA in reproductive age group [Source: Management of rheumatoid arthritis during pregnancy: challenges and solutions (Krause and Makol)[10]]

Abbreviations: RA, rheumatoid arthritis; MTX, methotrexate; LEF, leflunomide; DAS28, Disease Activity Score in 28 joints; NSAIDs, nonsteroidal anti-inflammatory drugs; GCs, glucocorticoids; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; SSZ, sulfasalazine; TNF, tumor necrosis factor; AZA, azathioprine

Except for patients with high disease activity, having a mild decrease in fecundity[16] and a moderate risk of prematurity and low birth weight, the course and outcome of pregnancy are generally favourable in RA patients[19].

3 Effect of the disease on pregnancy

Fertility/Family planning

Women with RA seem to have fewer children and older age at first birth than other women[22]. The ultimate number of children a woman with RA will have depends on multiple factors. A good per cent of patients consider RA to be impacting their family planning decisions in terms of their fear regarding the functional ability to take care of the child, medications and heritability of the disease and have fewer children than those who don't[22]. Another group of women thinking the disease and medications will negatively impact the child also seems to have fewer children compared to others.[23] On evaluation by anti-Mullerian hormone levels, it was found that the fertility issues in RA women are not related to reduced ovarian reserve [24]. Also, some large cohorts showed that those patients diagnosed with RA before conception were more likely to seek infertility treatment[25] and took more time to conceive[6, 25].

Pregnancy Outcomes

Multiple cohorts show delivery by caesarean section is more common among women with RA in a wide range of geographic regions[26–30] and is more common in those with moderate to severe disease activity[31].

Some studies reported increased pre-eclampsia risks[28, 30] but some not[26, 27, 29]. The difference may be due to different patient population selections or preeclampsia case ascertainment.

A lot of studies demonstrate preterm births seem to be associated more with RA patients[26–29, 32] but not all[30]. Disability measurement tools like the health assessment questionnaire (HAQ) were used in some studies and demonstrated the incidence of prematurity increases with increasing HAQ values[33].

Regarding variable data on low birth weights(LBW), many studies are showing a positive association[27, 28,

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

30, 34] and many didn't find any association[26, 29, 31]. Disease activity in the third trimester[31] and higher HAQ values[33] are demonstrated to be associated with LBW. These variable results may be because the differences in disease activities are not properly matched between studies.

Till now there is no data available showing an increase in congenital anomaly risk in infants of a woman with RA due to the disease activity[26, 28].

4 Guide for Medication Counselling

Even though there are many guidelines and safety profiles available for the drugs; most of them don't take into account the route of administration, dosage particulars, stage of pregnancy at which the drug was used etc[35]. Furthermore, there are many factors leading to the paucity of drug safety data on pregnancy, mainly the deliberate exclusion of pregnancy from most of the drug trials. So most of the data have a weaker level of evidence. Also, these patients are taking multiple drugs at a time which makes it difficult to attribute the fetal abnormality observed to a particular drug. Another concern is that the safety profile has been extrapolated from other autoimmune disorders like IBD and SLE; however, it is not very clear how much that can be applied to RA patients, especially when the dosage for the other diseases is different[36].

In contradiction to the old thoughts, a lesser number of pregnant patients with RA are getting spontaneous improvement in signs and symptoms during pregnancy. So most pregnant RA patients need some treatment as only a small minority achieve spontaneous remission. Moreover, a large majority develop flare-in symptoms in the postpartum period leading to rapid initiation of medical therapy[18– 21]. So it becomes necessary to counsel the patients about the safe usage of analgesics and DMARDs not only before and during pregnancy but also post-delivery.

The treatment of RA has been revolutionised in recent years. Novel drugs, such as biologics, and new strategies, such as "treat to target", have made a big difference for people with RA. However, many of these drugs are not well-studied or safe for pregnant or breastfeeding women[10].

With the evidence from human and animal data, the US FDA categorised drugs according to pregnancy risk (Table 1)[37]. This supports the treatment planning but is not an alternative to open discussions and shared decision-making, which is very critical in this scenario where risks and benefits of the treatment may be individualised.

Furthermore, through experience and feedback, the US FDA found that the pregnancy categories were confusing and lacked accuracy and consistency in terms of the degree of fetal risk. Most clinicians heavily rely on these categories and has been misinterpreted and misused in prescribing the drugs without knowing the underlying details which led the FDA to make such categories. Thus now the FDA believes a narrative structure explaining potential risks of drug exposure in human and animal studies will be a better guide than a category system and introduced a "final rule" to remove all pregnancy categories from all the drug labelling (effective from 30 June,2015). The final rule states that labelling should include the relevant information about pregnancy testing, infertility and contraception. It also orders to maintain a consistent format that provides information regarding the risks and benefits of the prescription drugs and/or the biological products used during pregnancy and lactation by females and males in their reproductive age group[10, 38]. These changes will help facilitate prescriber counselling for those patients with reproductive potential.

\

Therapy	FDA pregnancy category[1]	Toxicity concerns
NSAIDs	B	Concern for risk in third trimester exposure including closure of ductus arteriosus
Corticosteroids	B	Question of increased risk of cleft abnormalities
Sulfasalazine	B	No reported risk
TNFα inhibitors	B	Question of concerns for VACTERL abnormalities
Anakinra	B	Inadequate data
COX 2 inhibitors	C	Concern for risk in third trimester exposure including closure of ductus arteriosus
Hydroxychloroquine	C	No reported risk
Rituximab	C	Reports of hematologic abnormalities, infection
Abatacept	C	Inadequate data
Tocilizumab	C	Inadequate data
Tofacitinib	C	Inadequate data
Azathioprine	D	Rare reports of congenital abnormalities but overall not felt to increase risk
Methotrexate	X	Aminopterin syndrome
Leflunomide	X	Toxicity in animal studies

[1]US Food and Drug Administration pregnancy category [see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57]; A, controlled human studies show no risk; B, no evidence of risk in studies; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.
NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor; VACTERL, vertebral anomalies, anal atresia, cardiac defects, tracheoesophageal, renal, and limb abnormalities.

Table. 1 Summary of safety recommendations of therapies for rheumatoid arthritis in pregnancy. [Source: Use of DMARDs and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. (Krause and Makol)[123]]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

In the following subsections, we will be discussing the risks and benefits of the commonly used drugs and the best practice of their use in RA for a woman in her reproductive period (preconception, pregnancy and lactation) and also preconception recommendations for males. The US FDA recommendations were also reviewed given their previous widespread use.

4.1 ANTI-INFLAMMATORY DRUGS

4.1.1 Non-Steroidal Anti-Inflammatory Drugs(NSAIDs)

NSAIDs are a class of drugs that inhibit the production of prostaglandins(PGs) by inhibiting the cyclooxygenase (COX) enzyme [39]. Its use in pain management is ubiquitous owing to its effective anti-inflammatory and analgesic properties [40]. Although the recommendation in RA is to discontinue NSAIDs once the disease is controlled with DMARDs, a significant number of patients remain on NSAID use for pain relief[36].

NSAIDs come under Category B drug as per the US FDA (Table 1) for their use in pregnancy.

Even though it is a relatively safe option in managing pregnant RA patients, it needs to be used with caution, especially early in pregnancy and is contraindicated in the third trimester. Even though many studies are proving no association of NSAIDs with prematurity, low birth weight or congenital anomalies[41, 42], there are many studies suggesting increased risks of miscarriage, especially close to conception and more than 1 week of use[41, 43, 44]. So it has to be used with caution early in pregnancy. NSAID use late in pregnancy has an increased risk of premature closure of ductus arterioles, neonatal bleeding, reversible fatal renal function impairment, and oligohydramnios[45–49]. Hence most NSAIDs got FDA category C beyond 30 weeks of gestation. COX-2 inhibitors are category C in pregnancy risk according to the FDA, as data is scarce; hence not recommended during pregnancy to treat inflammatory symptoms in RA[45, 50].

Most NSAIDs can be used safely during lactation, although excreted in milk in low quantities. Aspirin is not recommended to use more than 100mg/day. Feeding immediately before drug intake limits drug exposure to infants to some extent[50–52].

In conclusion, NSAIDs including COX-2 inhibitors are contraindicated during the third trimester and can be used with caution before 24 weeks, with intermittent use and preferably those with short half-life[53].

4.1.2 Glucocorticoids (GCs)

Glucocorticoids (GCs) are steroid hormones, which are used in the treatment of a wide variety of diseases including inflammation, autoimmune diseases, and cancer[54]. As NSAIDs, GCs are also considered adjuncts for temporary control of disease activity but are used widely in a substantial number of patients[36].

Glucocorticoids come under Category B drug as per US-FDA(Table 1) for their use in pregnancy and are used frequently in managing RA during pregnancy[55].

Non-fluorinated GCs like prednisone, prednisolone and methylprednisolone can cross the placenta only in very low concentrations as they get metabolised in the placenta to an inactive metabolite before reaching the fetus. So they are relatively safe during pregnancy in low to moderate doses [56]. Fluorinated GCs like dexamethasone or betamethasone should be avoided in pregnant ladies (unless for a fatal indication) as they cross the placenta more efficiently with similar maternal and fetal concentrations[57, 58]. GCs have not shown any risks of miscarriage unlike NSAIDs[59]. Even though few human and animal studies showed mildly increased risk[60, 61] for cleft lip/palate in first-trimester use, many recent studies didn't find any correlation[62].

Corticosteroids are considered safe in lactation[63]. Secretion of prednisolone is less than 0.1% of the maternal dose; which is less than 10% of the endogenous cortisol level of an infant[52, 64].

In conclusion, GCs are a safe option in treating a pregnant RA patient, if necessary in the lowest possible dose to control the disease activity. Also, it is better to counsel the mother regarding minimal risks of oral clefts even though only variable risk studies are available along with close monitoring of blood pressure and sugar levels throughout the pregnancy.

4.2 SYNTHETIC DMARDS

4.2.1 Sulfasalazine

Sulfasalazine is a prodrug that consists of 5-aminosalicylic acid (mesalamine or mesalazine) and sulfapyridine, both linked by an azo bond. Its exact

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

mechanism of action is not fully understood[65]. It is frequently used in combination therapy for RA[66].

Sulfasalazine comes under Category B drug as per US-FDA(Table 1) for its use in pregnancy and is considered safe during pregnancy, even though there are some reports of increased incidence of cleft palate, neural tube defects and cardiovascular anomalies[67].

As it is a dihydrofolate reductase inhibitor, it is recommended to use extra folate supplementation; which is demonstrated to decrease the augmented risks of cardiovascular anomalies and cleft palate associated with folate antagonist usage during pregnancy[68].

Most of the information regarding the safety of sulfasalazine during pregnancy and lactation has been taken from studies in IBD patients using sulfasalazine during pregnancy. Even though it crosses the placenta and is found to have equal maternal and cord blood levels[69], it is considered safe during pregnancy as multiple studies are showing no increased risk of congenital anomalies, stillbirth, spontaneous abortion, preterm delivery or low birth weight[70–72]. Even though few case reports show adverse outcomes, it is difficult to attribute those to the drugs. A reversible congenital neutropenia was noted following maternal sulfasalazine given at a dose of 3g daily; (so it is not recommended beyond 2g per day)[73] and another one showing haemolytic anemia[74].

Sulfasalazine has been found only in very minimal amounts in breast milk, but its metabolite sulfapyridine has been found in around 30 to 60% of maternal serum levels. Nevertheless, it can be considered safe to breastfeed a healthy, full-term infant[52, 75, 76]. It is recommended to be avoided in lactating mothers of a premature, hyperbilirubinemic or G6PD deficient infant[77].

Sulfapyridine of sulfasalazine is known to impede spermatogenesis and can reduce motility and quality of sperm; which is reversible[78]. So it is recommended to discontinue sulfasalazine 3 months before attempting conception in male RA patients.

In conclusion, sulfasalazine can be used safely in pregnancy with balanced available evidence of safety. Folate supplementation should be encouraged during preconception and throughout pregnancy, as it is a strong dihydrofolate reductase inhibitor[79].

4.2.2 Hydroxychloroquine (HCQs)

Hydroxychloroquine is an anti-malarial drug with immunomodulatory activity when used as monotherapy or as combination therapy in treating rheumatoid arthritis[36, 66].

Hydroxychloroquine comes under Category C drug as per US-FDA(Table 1) for its use in pregnancy and can be safely used during pregnancy if indicated to control the disease activity (Table 1)

Most of the safety data of HCQ for RA are derived by extrapolating their use in SLE[10]. There are numerous studies stating no evidence of increased risk for spontaneous abortion, rates of live births, prematurity, fetal death or adverse fetal/ pregnancy outcome, including congenital anomalies[80–84]. Also, a recent study on the usage of HCQ in lupus pregnancies, suggested that the use of hydroxychloroquine has controlled the disease activity in the mother without any flairs and was able to decrease the dosage of prednisolone in the mother without any issues with the patient's health. Obstetric scores were also better and there were no congenital anomalies in children even at 1.5 to 3 years on neuro-ophthalmological/ auditory evaluation[85]. Another study by Park et al with extended follow-up (33 months) till childhood of the offspring of pregnant lupus mothers on HCQ revealed no abnormalities in children[86]. A recent study in refractory APA syndrome also showed better obstetrical outcomes with the addition of HCQs to the medications used[87]. Fetal toxicity reports were based on the studies with chloroquine (which has 2.5 times tissue deposition compared to hydroxychloroquine). No fetal toxicity has been reported with HCQ in doses used in the setting of rheumatoid arthritis or other connective tissue disorders (6.5 mg/kg body weight)[86]. The use of HCQ during pregnancy has been controversial due to retinal and ototoxicity after treatment with chloroquine[88]. HCQ has got similar concentration in maternal and cord blood of new-borns, suggesting its transplacental passage[89].

Only a trace amount of drug can be detected in breast milk, so it is considered safe for breastfeeding[88].

Even though HCQ crosses the placenta, there is no increased congenital malformation at a recommended daily dose of 200 to 400mg. Also long time, studies in

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

children were not able to detect any visual, hearing or developmental anomalies[75, 77].

4.2.3 Azathioprine

Azathioprine is a pro-drug that gets converted into 6-mercaptopurine (6-MP) by the purine metabolism pathway and it acts as a purine anti-metabolite [90]. As a purine analogue, it inhibits DNA synthesis and affects the cells with high proliferation(i.e., T and B lymphocytes)[91]. Even though Azathioprine is approved by the FDA for the treatment of rheumatoid arthritis, it is not frequently used with the availability of newer drugs.

Azathioprine (ASA) and 6-Mercaptopurine (6MP) fall under Category D drug as per US-FDA (Table 1) for their use in pregnancy, that is increased fetal risk present but the risk has to be weighed against potential benefits[92]. Safety data of AZA in pregnancy is mainly derived from studies in IBD and transplant patients. A recent Danish cohort study[93] stated that the children of mothers with Crohn's disease using ASA/6-MP are more likely to be born prematurely and can have congenital anomalies (occipital encephalocele, sternocleidomastoid anomalies and congenital cataract). Many other reports suggest no increased risk of anomalies[72, 94–97], but some show increased prematurity, low gestational age and birth weight[94], and reported are more likely due to the disease than drug[98].

Breastfeeding is contra-indicated traditionally in thiopurine treatment. However many recent studies show low 6MP levels in breast milk and concluded can be safely used during breastfeeding[99–101].

Even though azathioprine is considered Category D, recent studies confirm its safety and can be used in pregnancy if indicated after counselling about chances of minimal risk.

4.2.4 Methotrexate

Methotrexate is the methyl derivative of aminopterin (Folate antagonist- inhibits dihydrofolate reductase)[36] and is considered the anchor drug in managing rheumatoid arthritis and recommended to be the first DMARD to start given its long-term safety profile and effectiveness[66].

Initiating treatment for RA in females of the childbearing age group poses a dilemma because it comes under Category X drug as per US-FDA (Table 1) for its use in pregnancy, as it is an effective abortifacient and teratogen[77, 102–104].

Women who have exposure to high-dose methotrexate early in pregnancy are at high risk for 'aminopterin/methotrexate syndrome' characterised by CNS, skeletal and cardiac anomalies[105, 106]. Most of the earlier studies are based on high-dose usage in a chemotherapy setting[93], the prevalence of congenital anomalies with weekly low-dose exposure is not very clear[77]. Even though many studies stated the risks of congenital anomalies while using low dose (5-10mg weekly) methotrexate early in pregnancy were very less/minor/absent and with risks of spontaneous abortion[107–112], few case studies are showing severe aminopterin syndrome[105, 113] and other toxicity including skull abnormalities[114]. The sample size was less in all those studies and not able to come to a definite conclusion. Even with some safety profiles, we should not underestimate the risks of methotrexate in pregnancy because of severe congenital anomalies and developmental anomalies[10]. It is recommended to stop methotrexate immediately if the patient is diagnosed to be pregnant and these safety data can be used for counselling unintentional pregnancies. Because its active metabolite has a long half-life, it should be stopped at least 3 months before conception; and folic acid supplementation to be continued during that interval and throughout the pregnancy[112] and past exposure poses no negative effects.[107].

Methotrexate is found to be excreted in breast milk in low concentrations only but can be accumulated in the infant, hence contraindicated in lactation because of the theoretical risk[64, 77].

Even though there is no data on teratogenicity in the offspring of male patients on methotrexate[102], it is advised that the male partner should also stop methotrexate at least 3 months before attempting conception[115].

Therefore in pregnancy, methotrexate is absolutely contraindicated. For use in ladies in their childbearing age group, it is advisable to use two different contraceptive methods and to stop methotrexate 3 months before planned conception[116]. In cases of

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

unplanned pregnancy, while using methotrexate, it should be stopped immediately and sent to the patient for genetic counselling to decide on continuing pregnancy or for abortion.

4.2.5 Leflunomide

It is a pyrimidine antagonist having anti-proliferative activity with additional protein tyrosine kinase inhibition; used in treating moderate to severe RA[36, 117], especially in the setting of methotrexate intolerance[66].

It is found to be embryotoxic and teratogenic in many animal studies leading to growth retardation and cardiovascular, craniofacial, ophthalmic and skeletal malformations[117, 118]. Even though some human studies reported no increased risk of congenital malformation after first-trimester use followed by cholestyramine washout[77, 118], one study[119] showed a 12.5% higher risk of congenital anomaly (without any clear conclusion regarding causality). Due to limited studies in human pregnancies, leflunomide is classified under Category X drug as per the US FDA (Table 1) for its use in pregnancy.

It has a long half-life of 14-15 days, as it undergoes enterohepatic circulation its active metabolite takes up to 2 years for complete elimination from the body after cessation of the drug[50]. So it is recommended that when a woman or man (even though no evidence for men) planning to conceive should undergo a cholestyramine washout procedure with 8g cholestyramine three times daily for 11 days and the plasma levels to be checked twice 2 weeks apart and should be below 0.02mg/l. If above the level additional cholestyramine administration is recommended, and conception needs to be delayed for another 3 menstrual cycles after the elimination[50]. Drug level monitoring helps in counselling optimal timing for the pregnancy[120].

Leflunomide is secreted in breast milk. Even though data regarding safety are scarce[63]; it is contraindicated during lactation also[50, 121].

Leflunomide is so contraindicated during pregnancy and should be cautious in prescribing to women in the childbearing age group, due to its long retention even after stopping the drug. In an unplanned pregnancy with exposure to leflunomide, as in the case of methotrexate exposure; leflunomide should be stopped immediately and refer the patient for genetic counselling for discussion of risks and further planning. And leflunomide exposed patient should undergo a cholestyramine washout additionally.

4.3 BIOLOGIC DMARDS

Biological DMARDs are antibodies administered parenterally, reserved for treating severe RA refractory to standard treatment with conventional DMARDs. As these agents are relatively new, the safety data about them in humans and animals are limited. Most of the human data are derived from registries and studies in IBD[36]. As there is active transport of IgG of maternal antibodies through the placenta in the second and third trimester, they will be transported into fetal circulation from the second trimester, with increasing concentration if continued until birth, even more than maternal concentrations[122].

4.3.1 TNF-α inhibitors

TNF-α inhibitors are the class of biologics which are best studied. The currently available ones are infliximab, etanercept, adalimumab, golimumab and certolizumab. Infliximab is a chimeric monoclonal antibody, etanercept is a soluble receptor blocker and adalimumab, golimumab and certolizumab come under humanised TNF antibody[36]. TNF-α inhibitors are recommended for managing RA patients refractory to methotrexate alone or as a first-line drug when there are poor prognostic factors present[66].

All of them come under Category B drugs as per US-FDA (Table 1) for their use in pregnancy primarily due to the finding that they didn't cause any risks in animal studies.

Many controversies were raised after some case reports of congenital anomalies following TNF-α inhibitors during pregnancy[123], mainly VACTERL (vertebral defects, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal and limb abnormalities)[124, 125]. But more recent data were in contrast to these. Many studies came up later which showed no VACTERL association with TNF-α inhibitors exposure and also without increased risks of congenital malformations[126–135]. However, some studies showed borderline risks for congenital

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

anomalies[136]. Even though the risks of spontaneous abortions were not significant in many cohorts [128, 131, 136], some showed increased risks[126]. Some studies showed an increase in prematurity risks[136], but some couldn't confirm this[126, 128].

Anti-TNF-α antibodies (IgG) can be probably administered safely during the first trimester since IgG cannot cross the placenta during the first trimester. Transplacental transport of IgG starts only after the first trimester and increases mainly during the third trimester of pregnancy[137]. Etanercept has less transplacental passage compared to other complete antibodies and they are fusion proteins[128]. Certolizumab cannot be actively transported through the placenta as it doesn't have an Fc component, giving it a theoretical safety over other TNF-α inhibitors[138]. Infliximab and adalimumab have higher concentrations in infant and cord blood than mother[128].

As there is only very little transplacental passage of TNF-α inhibitor into fetal circulation during the first trimester, it is considered low risk to continue the drug preconception period and at least until pregnancy is confirmed. In the case of severe maternal disease, there are reported cases of TNF-α inhibitors given till the beginning of the third trimester, although long-term outcome studies in children are lacking.

Another concern regarding TNF-α inhibitors and other biologicals is the potential immunosuppression in infants after birth. A case of infant death due to disseminated BCG following vaccination in an infant of a mother who was on infliximab throughout pregnancy[139]. Therefore it is recommended to postpone live vaccine administration to infants till 6 months of age if there is TNF-α inhibitor exposure during pregnancy.

TNF-α inhibitors can be used while breastfeeding as very minimal transfer to breast milk is only shown for infliximab, adalimumab, etanercept and certolizumab[63].

In conclusion, even though recent studies discredited initial reports of VACTERL abnormalities; in terms of VACTERL or other congenital anomalies, most of the safety data obtained were based on women discontinuing TNF-α inhibitors in the first trimester and very little data exists about throughout pregnancy exposure. Hence risk benefit has to be assessed and explained before starting these drugs.

4.3.2 Rituximab

Rituximab is a monoclonal antibody against CD29 of B cells[36]. Rituximab is reserved for those patients who failed to respond to a combination of conventional DMARDs or TNF-α inhibitors[66]. There are studies where usage of rituximab in pregnancies has been recorded with a wide range of maternal indications with exposure to concomitant other teratogen mainly methotrexate, with few cases of prematurity, haematological abnormalities and infections in infant, neonatal death(only 1 case out of 153 pregnancies) and 2 reports of congenital anomalies(a clubfoot and a cardiac malformation)[140]. Another case series shows few reports of oesophageal atresia, prematurity and miscarriage[141, 142]. There are concerns regarding haematological abnormalities and infection in infants.

Due to lacking data about its secretion in breast milk, it is not advisable to use it during lactation[143].

It comes under Category C drug as per US-FDA (Table 1) for its use in pregnancy with limited available data. It is advisable to stop rituximab 12 months before conception due to its long half-life [123].

4.3.3 Abatacept

It is a cytotoxic T-lymphocyte antigen- 4 immunoglobulin fusion protein that selectively blocks T-cell co-stimulation by the CD80/CD86 pathway[92].

The largest series of 151 pregnancies with 86 live births (almost half were receiving methotrexate) with 40 spontaneous and 19 elective abortions showed 7 congenital anomalies including cleft lip, cardiac anomalies, trisomy 21(premature at 17 weeks and subsequent infant death), meningocele, skull malformations, pyloric stenosis[144].

As no data regarding secretion in breast milk, breastfeeding is contraindicated while on abatacept[143].

It comes under Category C drug as per US-FDA (Table 1) for its use in pregnancy with limited available data. It is recommended to stop abatacept 14 Weeks before conception (5 times half-life)[145]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

4.3.4 Anakinra

Anakinra is a recombinant Interlukin-1 (IL-1) receptor antagonist. Its use has been approved by the FDA for RA since 2001[123].

Even though the animal studies from the package insert, there were no harm to the fetus has been reported, and has to be used in pregnancy only if indicated[146]. In a study on women with cryopyrin-associated periodic syndromes with anakinra exposure, out of 9 births only one fatal death(one among the twin pregnancy) was recorded in the setting of renal agenesis with NLRP3 mutation, otherwise no adverse events or prematurity[147]. Also in 3 patients with Stills disease, anakinra exposure results in successful uneventful deliveries[148, 149].

Anakinra comes under Category B drug as per US-FDA (Table 1) for its use in pregnancy and little is known about its safety during pregnancy[146].

4.3.5 Tocilizumab

Tocilizumab is a monoclonal antibody against IL-6 receptors, thereby blocking downstream signalling. It was approved for treating RA in 2010 as monotherapy or in combination with methotrexate or other DMARDs[123].

As per the manufacturers' package insert, there is no reported teratogenicity in animal models (but increased abortion risks at very high doses have been observed)[150] A large report of pregnancies with tocilizumab exposure (33 pregnancies in 32 patients from 8 trials; 26 patients were also on MTX - with 7 spontaneous and 13 elective abortions) with 11 deliveries happened and 10 of them were healthy and 1 infant died due to ARDS, 3 days after birth[151]. Table 3 and Table 4 below.

Further from the Japanese registry with 6 pregnancies; there was one spontaneous abortion and the rest 5 healthy full-term deliveries without any congenital anomalies have been reported[152]. Another recent study with 61 tocilizumab exposed pregnancies; (there were 50 reported outcomes with 36 live births) without any congenital anomalies even though 9 spontaneous and 5 elective abortions were there[153].

Data regarding tocilizumab excretion in milk is not available hence not recommended to breastfeed while on therapy[154].

Due to the paucity of data, it is recommended to stop tocilizumab 3 months before attempting conception[36, 45] and considered as pregnancy category C by the US-FDA (Table 1).

4.3.6 Tofacitinib

Tofacitinib comes under the class Janus kinase (JAK) inhibitor and was recently approved by the FDA for treatment in RA in 2012[123].

Animal studies demonstrated teratogenicity and feticidal effects with a much higher dose than what is recommended in humans. There is no published data available regarding its exposure and pregnancy outcomes or breastfeeding [155]. It comes under Category C drug as per US-FDA (Table 1) for its use in pregnancy with limited available data.

4.4 AUTHOR'S VIEW

Authors view regarding the best practice of drug therapy in RA for a woman in her reproductive period (preconception, pregnancy and lactation) and also during preconception recommendation for males has been summarised in Table 2,

Medications preferred (If required)	Medications relatively safe (Needs individualized approach)	Medications contraindicated	Inadequate data to support on safety
Glucocorticoids (B)[a] NSAIDs (B)[b] Hydroxychloroquine (C) Sulfasalazine (B)	TNF-α inhibitors (B) Azathioprine (D)	Methotrexate (X) Leflunomide (X)	Anakinra (B) Abatacept (C) Tocilizumab (C) Tofacitinib (C) Rituximab (C)[c]

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

Notes: The US FDA pregnancy category for each drug is quoted in parenthesis:
A: controlled human studies show no risk
B: no evidence of risk in studies
C: risk cannot be ruled out
D: positive evidence of risk
X: contraindicated in pregnancy.
[a]Counselling advised regarding possible cleft lip/palate abnormalities. [b]Avoid in third trimester due to risk of premature closure of ductus arteriosus. [c]Recommendation is to avoid in pregnancy due to hematologic abnormalities and infection risk.
Abbreviations: TNF, tumor necrosis factor; NSAIDs, nonsteroidal anti-inflammatory drugs; FDA, Food and Drug Administration.

Table 2. Recommendation during preconception and pregnancy

Medications preferred (If required)	Inadequate data to support on safety	Medications contraindicated
Glucocorticoids NSAIDs Hydroxychloroquine Sulfasalazine [a]	TNF-α inhibitors Anakinra Abatacept Rituximab Tocilizumab Tofacitinib	Methotrexate Leflunomide Azathioprine [b]
Notes: [a]Caution is advised in the setting of prematurity, hyperbilirubinemia, and glucose-6-phosphate dehydrogenase deficiency. [b]Avoidance is recommended by the manufacturer and expert opinion which is primarily based on theoretical risk. **Abbreviations:** TNF, tumor necrosis factor; NSAIDs, nonsteroidal anti-inflammatory drugs.		

Table 3. Recommendation during lactation

Drugs	Recommendations
Methotrexate	Hold 3 months prior to contraception due to sperm life cycle
Sulfasalazine	If difficulty with fertility, consider holding as it has been associated with reversible infertility
Azathioprine	No data to suggest adverse outcomes
Leflunomide	Insufficient data, but no adverse outcomes reported
TNF- α inhibitors	Varied data regarding spermatogenesis but overall favourable outcomes
Rituximab	Insufficient data, but adverse outcomes reported
Abatacept	Insufficient data, but adverse outcomes reported

Table 3. Preconception recommendation for Men

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

5 Conclusion

Rheumatologists/Physicians/Orthopaedicians/Obstetricians play a pivotal role, in supporting and guiding patients, with arthritis (RA) who are of childbearing age and are contemplating starting a family. It is essential to manage the disease using disease-modifying drugs (DMARDs) and biologics to prevent joint damage and long-term disability. Fortunately, the range of treatment options is expanding as we deepen our understanding of RA's underlying mechanisms. Healthcare providers should be able to educate patients, about the risks and advantages of these medications tailoring treatment plans for each individual to promote a pregnancy and ensure the well-being of the newborn. This can be achieved by choosing the most appropriate disease-modifying medicine based on patients' desire for childbearing, educating about suitable contraception, timing the pregnancy in very stable RA, adequate follow-up during pregnancy so that the disease remains stable, postpartum starting an appropriate therapy to prevent severe flares which may occur with the patient's wish to breastfeed her child taken into consideration. Educating men is also essential since certain drugs can cause reversible sterility, and impair fertility or embryotoxicity. Discussion of safety data shortage concerning the new medications needs to be included because the human experience is limited at the moment and it only covers accidental exposure during conception or early stage of pregnancy, and mostly involves cases in animal and preclinical data. The prioritization of an early and comprehensive dialogue between the patients cannot be overvalued.

6 Acknowledgement

The authors conducted the study design, data collection, data analysis, and manuscript preparation independently, without external help.

7 Funding

No particular financial support from any public, private, or non-profit funding entities was allocated for this study.

8 Conflict of interest statement

The authors declare that they have no financial interests related to the study that need to be disclosed.

References

[1] Sparks, J.A.: Rheumatoid arthritis. Annals of Internal Medicine **170**(1), 1 (2019) https://doi.org/ 10.7326/aitc201901010

[2] Jandu, J., Chauhan, K., Goyal, A., Bansal, P., Al-Dhahir, M.: Rheumatoid Arthritis - StatPearls - NCBI Bookshelf, pp. 1–10 (2020)

[3] Lee, D.M., Weinblatt, M.E.: Rheumatoid arthritis. The Lancet **358**(9285), 903–911 (2001) https: //doi.org/10.1016/s0140-6736(01)06075-5

[4] Firestein GS, K.W.: elley's textbook of rheumatology, 8th edn. Saunders/Elsevier, Philadelphia, PA, pp. 1–2064 (2009)

[5] Cross, M., Smith, E., Hoy, D., Carmona, L., Wolfe, F., Vos, T., Williams, B., Gabriel, S., Lassere, M., Johns, N., *et al.*: The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Annals of the rheumatic diseases **73**(7), 1316–1322 (2014)

[6] Brouwer, J., Hazes, J.M., Laven, J.S., Dolhain, R.J.: Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Annals of the rheumatic diseases **74**(10), 1836–1841 (2015)

[7] Jong, P.H., Dolhain, R.J.: Fertility, pregnancy, and lactation in rheumatoid arthritis. Rheumatic Disease Clinics **43**(2), 227–237 (2017)

[8] Ince-Askan, H., Dolhain, R.J.: Pregnancy and rheumatoid arthritis. Best practice & research Clinical rheumatology **29**(4-5), 580–596 (2015)

[9] Østensen, M., Wallenius, M.: Fertility and pregnancy in rheumatoid arthritis. Indian Journal of Rheumatology **11**(Suppl 2), 122–127 (2016)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

[10] Krause, M.L., Makol, A.: Management of rheumatoid arthritis during pregnancy: challenges and solutions. Open access rheumatology: research and reviews, 23–36 (2016)

[11] Hench, P., *et al.*: The ameliorating effect of pregnancy on chronic atrophic (infectious rheumatoid) arthritis, fibrositis, and intermittent hydrarthrosis. In: Mayo Clin Proc, vol. 13 (1938)

[12] Golding, A., Haque, U.J., Giles, J.T.: Rheumatoid arthritis and reproduction. Rheumatic Disease Clinics of North America **33**(2), 319–343 (2007)

[13] Hargreaves, E.: A survey of rheumatoid arthritis in west cornwall: a report to the empire rheumatism council. Annals of the rheumatic diseases **17**(1), 61 (1958)

[14] Oka, M.: Effect of pregnancy on the onset and course of rheumatoid arthritis. Annals of the rheumatic diseases **12**(3), 227 (1953)

[15] Klipple, G.L., Cecere, F.A.: Rheumatoid arthritis and pregnancy. Rheumatic Disease Clinics of North America **15**(2), 213–239 (1989)

[16] Nelson, J.L., Hughes, K.A., Smith, A.G., Nisperos, B.B., Branchaud, A.M., Hansen, J.A.: Maternalfetal disparity in hla class ii alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. New England Journal of Medicine **329**(7), 466–471 (1993)

[17] Østensen, M., Aune, B., Husby, G.: Effect of pregnancy and hormonal changes on the activity of rheumatoid arthritis. Scandinavian journal of rheumatology **12**(2), 69–72 (1983)

[18] Man, Y.A., Dolhain, R.J., Hazes, J.M.: Disease activity or remission of rheumatoid arthritis before, during and following pregnancy. Current opinion in rheumatology **26**(3), 329–333 (2014)

[19] Østensen, M., Villiger, P.M.: The remission of rheumatoid arthritis during pregnancy. In: Seminars in Immunopathology, vol. 29, pp. 185–191 (2007). Springer

[20] Nelson, J.L., Østensen, M.: Pregnancy and rheumatoid arthritis. Rheumatic disease clinics of North America **23**(1), 195–212 (1997)

[21] Barrett, J.H., Brennan, P., Fiddler, M., Silman, A.J.: Does rheumatoid arthritis remit during pregnancy and relapse postpartum?: Results from a nationwide study in the united kingdom performed prospectively from late pregnancy. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology **42**(6), 1219–1227 (1999)

[22] Katz, P.P.: Childbearing decisions and family size among women with rheumatoid arthritis. Arthritis Care amp; Research **55**(2), 217–223 (2006) https://doi.org/10.1002/art.21859

[23] Clowse, M.E., Chakravarty, E., Costenbader, K.H., Chambers, C., Michaud, K.: Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. Arthritis care & research **64**(5), 668–674 (2012)

[24] Brouwer, J., Laven, J.S., Hazes, J.M., Schipper, I., Dolhain, R.J.: Levels of serum anti–mu¨llerian hormone, a marker for ovarian reserve, in women with rheumatoid arthritis. Arthritis care & research **65**(9), 1534–1538 (2013)

[25] Jawaheer, D., Zhu, J.L., Nohr, E.A., Olsen, J.: Time to pregnancy among women with rheumatoid arthritis. Arthritis & Rheumatism **63**(6), 1517–1521 (2011)

[26] Wallenius, M., Salvesen, K.˚A., Daltveit, A.K., Skomsvoll, J.F.: Rheumatoid arthritis and outcomes in first and subsequent births based on data from a national birth registry. Acta obstetricia et gynecologica Scandinavica **93**(3), 302–307 (2014)

[27] Wallenius, M., Skomsvoll, J.F., Irgens, L.M., Salvesen, K.˚A., Nordv˚ag, B.Y., Koldingsnes, W., Mikkelsen, K., Kaufmann, C., Kvien, T.K.: Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. Arthritis & Rheumatism **63**(6), 1534–1542 (2011)

[28] Nørgaard, M., Larsson, H., Pedersen, L., Granath, F., Askling, J., Kieler, H., Ekbom, A., Sørensen, H.T., Stephansson, O.: Rheumatoid arthritis and birth outcomes: a danish and swedish nationwide prevalence study. Journal of internal medicine **268**(4), 329–337 (2010)

[29] Reed, S.D., Vollan, T.A., Svec, M.A.: Pregnancy outcomes in women with rheumatoid arthritis in washington state. Maternal and child health journal **10**, 361–366 (2006)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

[30] Lin, H.-C., Chen, S.-F., Lin, H.-C., Chen, Y.-H.: Increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis: a nationwide population-based study. Annals of the Rheumatic Diseases **69**(4), 715–717 (2010)

[31] Man, Y.A., Hazes, J.M., Heide, H., Willemsen, S.P., Groot, C.J., Steegers, E.A., Dolhain, R.J.: Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology **60**(11), 3196–3206 (2009)

[32] Rom, A.L., Wu, C.S., Olsen, J., Kjærgaard, H., Jawaheer, D., Hetland, M.L., Vestergaard, M., Mørch, L.S.: Fetal growth and preterm birth in children exposed to maternal or paternal rheumatoid arthritis: a nationwide cohort study. Arthritis & Rheumatology **66**(12), 3265–3273 (2014)

[33] Bharti, B., Lee, S.J., Lindsay, S.P., Wingard, D.L., Jones, K.L., Lemus, H., Chambers, C.D.: Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the organization of teratology information specialists autoimmune diseases in pregnancy project. The Journal of rheumatology **42**(8), 1376–1382 (2015)

[34] Bowden, A.P., Barrett, J.H., Fallow, W., Silman, A.J.: Women with inflammatory polyarthritis have babies of lower birth weight. The Journal of rheumatology **28**(2), 355–359 (2001)

[35] Kennedy, D.: Classifying drugs in pregnancy. Australian Prescriber **37**(2) (2014)

[36] Ngian, G.-S., Briggs, A.M., Ackerman, I.N., Van Doornum, S.: Safety of anti-rheumatic drugs for rheumatoid arthritis in pregnancy and lactation. International Journal of Rheumatic Diseases **19**(9), 834–843 (2016)

[37] Food, U.: Drug administration code of federal regulations title 21. Department of Health and Human Services, ed. 21CFR20157. Washington: US Food and Drug Administration (2014)

[38] Food, Drug Administration, H., *et al.*: Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. final rule. Federal Register **79**(233), 72063–72103 (2014)

[39] Crofford, L.J.: Firestein & Kelley's textbook of rheumatology. Elsevier Philadelphia, PA (2021)

[40] Crofford, L.J.: Use of nsaids in treating patients with arthritis. Arthritis research & therapy **15**, 1–10 (2013)

[41] Nielsen, G.L., Sørensen, H.T., Larsen, H., Pedersen, L.: Risk of adverse birth outcome and miscarriage in pregnant users of non-steroidal anti-inflammatory drugs: population based observational study and case-control study. BMJ: British Medical Journal **322**(7281), 266 (2001)

[42] Nezvalov´a-Henriksen, K., Spigset, O., Nordeng, H.: Effects of ibuprofen, diclofenac, naproxen, and piroxicam on the course of pregnancy and pregnancy outcome: a prospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology **120**(8), 948–959 (2013)

[43] Nakhai-Pour, H.R., Broy, P., Sheehy, O., B´erard, A.: Use of nonaspirin nonsteroidal antiinflammatory drugs during pregnancy and the risk of spontaneous abortion. Cmaj **183**(15), 1713–1720 (2011)

[44] Li, D.-K., Liu, L., Odouli, R.: Exposure to non-steroidal anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. Bmj **327**(7411), 368 (2003)

[45] Østensen, M., F¨orger, F.: Management of ra medications in pregnant patients. Nature Reviews Rheumatology **5**(7), 382–390 (2009)

[46] Momma, K., Takeuchi, H.: Constriction of fetal ductus arteriosus by non-steroidal antiinflammatory drugs. Prostaglandins **26**(4), 631–643 (1983)

[47] Momma, K., Hagiwara, H., Konishi, T.: Constriction of fetal ductus arteriosus by non-steroidal anti-inflammatory drugs: study of additional 34 drugs. Prostaglandins **28**(4), 527–536 (1984)

[48] Koren, G., Florescu, A., Costei, A.M., Boskovic, R., Moretti, M.E.: Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a metaanalysis. Annals of Pharmacotherapy **40**(5), 824–829 (2006)

[49] Takahashi, Y., Roman, C., Chemtob, S., Tse, M.M., Lin, E., Heymann, M.A., Clyman, R.I.: Cyclooxygenase-2 inhibitors constrict the fetal

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

lamb ductus arteriosus both in vitro and in vivo. American journal of physiology-Regulatory, integrative and comparative physiology **278**(6), 1496–1505 (2000)

[50] Temprano, K.K., Bandlamudi, R., Moore, T.L.: Antirheumatic drugs in pregnancy and lactation. In: Seminars in Arthritis and Rheumatism, vol. 35, pp. 112–121 (2005). Elsevier

[51] Ostensen, M., Eigenmann, G.O.: Etanercept in breast milk. The Journal of rheumatology **31**(5), 1017–1018 (2004)

[52] Drugs, A.A., *et al.*: Transfer of drugs and other chemicals into human milk. Pediatrics **108**(3), 776–789 (2001)

[53] Makol, A., Wright, K., Amin, S.: Rheumatoid arthritis and pregnancy: safety considerations in pharmacological management. Drugs **71**, 1973–1987 (2011)

[54] Timmermans, S., Souffriau, J., Libert, C.: A general introduction to glucocorticoid biology. Frontiers in Immunology **10** (2019) https://doi.org/10.3389/fimmu.2019.01545

[55] Kuriya, B., Hern&39;andez-D&39;ıaz, S., Liu, J., Bermas, B.L., Daniel, G., Solomon, D.H.: Patterns of medication use during pregnancy in rheumatoid arthritis. Arthritis Care & Research **63**(5), 721–728 (2011)

[56] Bermas, B., et al.: Rheumatoid arthritis and pregnancy. UpToDate2012 (2010)

[57] Breur, J., Visser, G., Kruize, A., Stoutenbeek, P., Meijboom, E.: Treatment of fetal heart block with maternal steroid therapy: case report and review of the literature. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology **24**(4), 467–472 (2004)

[58] Ogueh, O., Johnson, M.: The metabolic effect of antenatal corticosteroid therapy. Human reproduction update **6**(2), 169–176 (2000)

[59] Bjørn, A.-M.B., Nielsen, R.B., Nørgaard, M., Nohr, E.A., Ehrenstein, V.: Risk of miscarriage among users of corticosteroid hormones: a population-based nested case- control study. Clinical Epidemiology, 287–294 (2013)

[60] Park-Wyllie, L., Mazzotta, P., Pastuszak, A., Moretti, M.E., Beique, L., Hunnisett, L., Friesen, M.H., Jacobson, S., Kasapinovic, S., Chang, D., *et al.*: Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology **62**(6), 385–392 (2000)

[61] Schardein, J.: Chemically Induced Birth Defects. CRC Press, ??? (2000)

[62] Gur, C., Diav-Citrin, O., Shechtman, S., Arnon, J., Ornoy, A.: Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. Reproductive toxicology **18**(1), 93–101 (2004)

[63] Skorpen, C.G., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers, C., Da Silva, J., Nelson-Piercy, C., Cetin, I., Costedoat-Chalumeau, N., *et al.*: The eular points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the rheumatic diseases **75**(5), 795–810 (2016)

[64] Østensen, M., Motta, M.: Therapy insight: the use of antirheumatic drugs during nursing. Nature clinical practice Rheumatology **3**(7), 400–406 (2007)

[65] Choi J, F.A.: Sulfasalazine. In: StatPearls [Internet] (2022). Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557809/

[66] Singh, J.A., Furst, D.E., Bharat, A., Curtis, J.R., Kavanaugh, A.F., Kremer, J.M., Moreland, L.W., O'Dell, J., Winthrop, K.L., Beukelman, T., Bridges, S.L., Chatham, W.W., Paulus, H.E., Suarezalmazor, M., Bombardier, C., Dougados, M., Khanna, D., King, C.M., Leong, A.L., Matteson, E.L., Schousboe, J.T., Moynihan, E., Kolba, K.S., Jain, A., Volkmann, E.R., Agrawal, H., Bae, S., Mudano, A.S., Patkar, N.M., Saag, K.G.: 2012 update of the 2008 american college of rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care amp;amp; Research **64**(5), 625–639 (2012) https://doi.org/10.1002/acr.21641

[67] Mogadam, M., Dobbins III, W.O., Korelitz, B.I., Ahmed, S.W.: Pregnancy in inflammatory bowel disease: effect of sulfasalazine and corticosteroids on fetal outcome. Gastroenterology **80**(1), 72–76 (1981)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

[68] Hern´andez-D´ıaz, S., Werler, M., Walker, A., Mitchell, A.: Folic acid antagonists during pregnancy and the risk of birth defects. The New England journal of medicine **343**, 1608–14 (2000) https://doi.org/10.1056/NEJM200011303432204

[69] Jarnerot, G., Into-Malmberg, M.-B., Esbjorner, E.: Placental transfer of sulphasalazine and sulphapyridine and some of its metabolites. Scandinavian journal of gastroenterology **16**(5), 693–697 (1981)

[70] Nørg˚ard, B., Czeizel, A., Rockenbauer, M., Olsen, J., Sørensen, H.T.: Population-based case control study of the safety of sulfasalazine use during pregnancy. Alimentary pharmacology & therapeutics **15**(4), 483–486 (2001)

[71] Rahimi, R., Nikfar, S., Rezaie, A., Abdollahi, M.: Pregnancy outcome in women with inflammatory bowel disease following exposure to 5- aminosalicylic acid drugs: a meta-analysis. Reproductive toxicology **25**(2), 271–275 (2008)

[72] Moskovitz, D.N., Bodian, C., Chapman, M.L., Marion, J.F., Rubin, P.H., Scherl, E., Present, D.H.: The effect on the fetus of medications used to treat pregnant inflammatory bowel-disease patients. Official journal of the American College of Gastroenterology— ACG **99**(4), 656–661 (2004)

[73] Levi, S., Liberman, M., Levi, A., Bjarnason, I.: Reversible congenital neutropenia associated with maternal sulphasalazine therapy. European journal of pediatrics **148**, 174–175 (1988)

[74] Bokstrom, H., Holst, R.-M., Hafstrom, O., Swolin, B., Louise Johansson, M., Brunlof, G., Hedner, T.: Fetal hemolytic anemia associated with maternal sulfasalazine therapy during pregnancy. Acta obstetricia et gynecologica Scandinavica **85**(1), 118–121 (2006)

[75] Gotestam Skorpen, C., Hoeltzenbein, M., Tincani, A., Fischer-Betz, R., Elefant, E., Chambers,

C., Silva, J., Nelson-Piercy, C., Cetin, I., Costedoat-Chalumeau, N., Dolhain, R., Forger, F., Khamashta, M., Ruiz-Irastorza, G., Zink, A., Vencovsky, J., Cutolo, M., Caeyers, N., Zumbuhl, C., Østensen, M.: The eular points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Annals of the Rheumatic Diseases **75**(5), 795–810 (2016) https://doi.org/10.1136/annrheumdis-2015-208840

[76] Branski D, G.E.H.H.L.R.A.A. Kerem E: Bloody diarrhea–a possible complication of sulfasalazine transferred through human breast milk. Journal of pediatric gastroenterology and nutrition **5**(2), 316–317 (1986)

[77] Østensen, M., Khamashta, M., Lockshin, M., Parke, A., Brucato, A., Carp, H., Doria, A., Rai, R., Meroni, P., Cetin, I., Derksen, R., Branch, W., Motta, M., Gordon, C., Ruiz-Irastorza, G., Spinillo, A., Friedman, D., Cimaz, R., Czeizel, A., Piette, J., Cervera, R., Levy, R.A., Clementi, M., De Carolis, S., Petri, M., Shoenfeld, Y., Faden, D., Valesini, G., Tincani, A. Arthritis Research amp;amp; Therapy **8**(3), 209 (2006) https://doi.org/10.1186/ar1957

[78] O'Morain, C., Smethurst, P., Dore, C.J., Levi, A.J.: Reversible male infertility due to sulphasalazine: studies in man and rat. Gut **25**(10), 1078–1084 (1984) https://doi.org/10.1136/gut. 25.10.1078

[79] Jansen, G., Heijden, J., Oerlemans, R., Lems, W.F., Ifergan, I., Scheper, R.J., Assaraf, Y.G., Dijkmans, B.A.: Sulfasalazine is a potent inhibitor of the reduced folate carrier: implications for combination therapies with methotrexate in rheumatoid arthritis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology **50**(7), 2130–2139 (2004)

[80] Sperber, K., Hom, C., Chao, C.P., Shapiro, D., Ash, J.: Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatric Rheumatology **7**(1) (2009) https://doi.org/10.1186/1546-0096-7-9

[81] Costedoat-Chalumeau, N., Amoura, Z., Duhaut, P., Huong, D.L.T., Sebbough, D., Wechsler, B., Vauthier, D., Denjoy, I., Lupoglazoff, J., Piette, J.: Safety of hydroxychloroquine in pregnant patients with connective tissue diseases: A study of one hundred thirty-three cases compared with a control group. Arthritis amp;amp; Rheumatism **48**(11), 3207–3211 (2003) https://doi.org/10.1002/art.11304

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

[82] Diav-Citrin, O., Blyakhman, S., Shechtman, S., Ornoy, A.: Pregnancy outcome following in utero exposure to hydroxychloroquine: A prospective comparative observational study. Reproductive Toxicology **39**, 58–62 (2013) https://doi.org/10.1016/j.reprotox.2013.04.005

[83] Buchanan, N.M., Toubi, E., Khamashta, M.A., Lima, F., Kerslake, S., Hughes, G.R.: Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. Annals of the Rheumatic Diseases **55**(7), 486–488 (1996) https://doi.org/10.1136/ard.55.7.486

[84] Clowse, M.E.B., Magder, L., Witter, F., Petri, M.: Hydroxychloroquine in lupus pregnancy. Arthritis amp;amp; Rheumatism **54**(11), 3640–3647 (2006) https://doi.org/10.1002/art.22159

[85] Levy, R.A., Vilela, V.S., Cataldo, M.J., Ramos, R.C., Duarte, J.L., Tura, B.R., Albuquerque, E.M., Jesu´s, N.R.: Hydroxychloroquine (hcq) in lupus pregnancy: double-blind and placebo-controlled study. Lupus **10**(6), 401–404 (2001) https://doi.org/10.1191/096120301678646137

[86] Parke, A., West, B.: Hydroxychloroquine in pregnant patients with systemic lupus erythematosus. J. Rheumatol. **23**(10), 1715–1718 (1996)

[87] De Carolis, S., Botta, A., Salvi, S., Pasquo, E., Del Sordo, G., Garufi, C., Lanzone, A., De Carolis, M.P.: Is there any role for the hydroxychloroquine (hcq) in refractory obstetrical antiphospholipid syndrome (aps) treatment? Autoimmunity Reviews **14**(9), 760–762 (2015) https://doi.org/10.1016/j.autrev.2015.04.010

[88] Costedoat-Chalumeau, N., Amoura, Z., Huong, D.L.T., Lechat, P., Piette, J.-C.: Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. review of the literature. Autoimmunity Reviews **4**(2), 111–115 (2005) https://doi.org/10.1016/j.autrev.2004.11.009

[89] Costedoat-Chalumeau, N., Amoura, Z., Aymard, G., Hong, D.L.T., Wechsler, B., Vauthier, D., Dermer, M.E., Darbois, Y., Piette, J.: Evidence of transplacental passage of hydroxychloroquine in humans. Arthritis amp;amp; Rheumatism **46**(4), 1123–1124 (2002) https://doi.org/10.1002/art. 10150

[90] Schram, M.E., Borgonjen, R.J., Bik, C.M., Schroeff, J.G., Everdingen, J.J., Spuls, P.I., *et al.*: Offlabel use of azathioprine in dermatology: a systematic review. Archives of dermatology **147**(4), 474–488 (2011)

[91] Sidbury, R., Davis, D.M., Cohen, D.E., Cordoro, K.M., Berger, T.G., Bergman, J.N., Chamlin, S.L., Cooper, K.D., Feldman, S.R., Hanifin, J.M., *et al.*: Guidelines of care for the management of atopic dermatitis: section 3. management and treatment with phototherapy and systemic agents. Journal of the American Academy of Dermatology **71**(2), 327–349 (2014)

[92] Hazes, J.M.W., Coulie, P.G., Geenen, V., Vermeire, S., Carbonnel, F., Louis, E., Masson, P., De Keyser, F.: Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. Rheumatology **50**(11), 1955–1968 (2011) https://doi.org/10. 1093/rheumatology/ker302

[93] Nørg˚ard, B., Pedersen, L., Christensen, L.A., Sørensen, H.T.: Therapeutic drug use in women with crohn39;s disease and birth outcomes: a danish nationwide cohort study. Official journal of the American College of Gastroenterology—ACG **102**(7), 1406–1413 (2007)

[94] Goldstein, L.H., Dolinsky, G., Greenberg, R., Schaefer, C., Cohen-Kerem, R., Diav-Citrin, O., Malm, H., Reuvers-Lodewijks, M.E., Tonningen-van Driel, M.M., Arnon, J., Ornoy, A., Clementi, M., Di Gianantonio, E., Koren, G., Braunstein, R., Berkovitch, M.: Pregnancy outcome of women exposed to azathioprine during pregnancy. Birth Defects Research Part A: Clinical and Molecular Teratology **79**(10), 696–701 (2007) https://doi.org/10.1002/bdra.20399

[95] Ban, L., Tata, L.J., Fiaschi, L., Card, T.: Limited risks of major congenital anomalies in children of mothers with ibd and effects of medications. Gastroenterology **146**(1), 76–84 (2014) https://doi.org/10.1053/j.gastro.2013.09.061

[96] Alstead, E.M., Ritchie, J.K., Lennard-Jones, J.E., Farthing, M.J.G., Clark, M.L.: Safety of azathioprine in pregnancy in inflammatory bowel disease. Gastroenterology **99**(2), 443–446

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

(1990) https://doi.org/10.1016/0016-5085(90)91027-4

[97] Polifka, J.E., Friedman, J.M.: Teratogen update: Azathioprine and 6-mercaptopurine. Teratology **65**(5), 240–261 (2002) https://doi.org/10.1002/tera.10043

[98] Boer, N.K.H., Jarbandhan, S.V.A., Graaf, P., Mulder, C.J.J., Elburg, R.M., Bodegraven, A.A.: Azathioprine use during pregnancy: Unexpected intrauterine exposure to metabolites. The American Journal of Gastroenterology **101**(6), 1390–1392 (2006) https://doi.org/10.1111/j.1572-0241.2006.00538.x

[99] Sau, A., Clarke, S., Bass, J., Kaiser, A., Marinaki, A., Nelson-Piercy, C.: Azathioprine and breastfeeding—is it safe? BJOG: An International Journal of Obstetrics amp;amp; Gynaecology **114**(4), 498–501 (2007) https://doi.org/10.1111/j.1471-0528.2006.01232.x

[100] CHRISTENSEN, L.A., DAHLERUP, J.F., NIELSEN, M.J., FALLINGBORG, J.F., SCHMIEGELOW, K.: Azathioprine treatment during lactation. Alimentary Pharmacology amp;amp; Therapeutics **28**(10), 1209–1213 (2008) https://doi.org/10.1111/j.1365-2036.2008.03843.x

[101] Zelinkova, Z., De Boer, I.P., Van Dijke, M.J., Kuipers, E.J., Van Der Woude, C.J.: Azathioprine treatment during lactation. Alimentary Pharmacology amp;amp; Therapeutics **30**(1), 90–91 (2009) https://doi.org/10.1111/j.1365-2036.2009.03996.x

[102] Weber-Schoendorfer, C., Chambers, C., Wacker, E., Beghin, D., Bernard, N., Shechtman, S., Johnson, D., Cuppers-Maarschalkerweerd, B., Pistelli, A., Clementi, M., Winterfeld, U., Eleftheriou, G., Pupco, A., Kao, K., Malm, H., Elefant, E., Koren, G., Vial, T., Ornoy, A., Meister, R., Schaefer, C.: Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: A prospective multicenter cohort study. Arthritis amp;amp; Rheumatology **66**(5), 1101–1110 (2014) https://doi.org/10.1002/art.38368

[103] Schaff, E.A., Penmetsa, U., Eisinger, S.H., Franks, P.: Methotrexate. a single agent for early abortion. J. Reprod. Med. **42**(1), 56–60 (1997)

[104] Hausknecht, R.U.: Methotrexate and misoprostol to terminate early pregnancy. New England Journal of Medicine **333**(9), 537–540 (1995) https://doi.org/10.1056/nejm199508313330901

[105] Buckley, L.M., Bullaboy, C.A., Leichtman, L., Marquez, M.: Multiple congenital anomalies associated with weekly low-dose methotrexate treatment of the mother. Arthritis amp;amp; Rheumatism **40**(5), 971–973 (1997) https://doi.org/10.1002/art.1780400527

[106] Hyoun, S.C., Obi˘can, S.G., Scialli, A.R.: Teratogen update: Methotrexate. Birth Defects Research Part A: Clinical and Molecular Teratology **94**(4), 187–207 (2012) https://doi.org/10.1002/bdra. 23003

[107] Ostensen, M., Hartmann, H., Salvesen, K.: Low dose weekly methotrexate in early pregnancy. a case series and review of the literature. J. Rheumatol. **27**(8), 1872–1875 (2000)

[108] Østensen, M., Esebeck, M., Villiger, P.M.: Therapy with immunosuppressive drugs and biological agents and use of contraception in patients with rheumatic disease. J. Rheumatol. **34**(6), 1266–1269 (2007)

[109] Lewden, B., Vial, T., Elefant, E., Nelva, A., Carlier, P., Descotes, J., French Network of Regional Pharmacovigilance Centers: Low dose methotrexate in the first trimester of pregnancy: results of a french collaborative study. J. Rheumatol. **31**(12), 2360–2365 (2004)

[110] Kozlowski, R.D., Steinbrunner, J.V., MacKenzie, A.H., Clough, J.D., Wilke, W.S., Segal, A.M.: Outcome of first-trimester exposure to low-dose methotrexate in eight patients with rheumatic disease. The American Journal of Medicine **88**(6), 589–592 (1990) https://doi.org/10.1016/ 0002-9343(90)90522-f

[111] Chakravarty, E.F., Sanchez-Yamamoto, D., Bush, T.M.: The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. J. Rheumatol. **30**(2), 241–246 (2003)

[112] Mart´ınez Lopez, J.A., Loza, E., Carmona, L.: Systematic review on the safety of methotrexate

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

in rheumatoid arthritis regarding the reproductive system (fertility,pregnancy, and breastfeeding). Clin. Exp. Rheumatol. **27**(4), 678–684 (2009)

[113] Mart´ın, M.C., Barbero, P., Groisman, B., Aguirre, M., Koren, G.: Methotrexate embryopathy after exposure to low weekly doses in early pregnancy. Reproductive Toxicology **43**, 26–29 (2014) https://doi.org/10.1016/j.reprotox.2013.10.005

[114] Powell, H.R., Ekert, H.: Methotrexate-induced congenital malformations. Medical Journal of Australia **2**(21), 1076–1077 (1971) https://doi.org/10.5694/j.1326-5377.1971.tb92712.x

[115] Swain, S., Jena, P.: Current understanding of rheumatoid arthritis therapy in pregnancy. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 3275–3279 (2016) https://doi.org/10.18203/2320-1770.ijrcog20163402

[116] Visser, K., Katchamart, W., Loza, E., Martinez-Lopez, J.A., Salliot, C., Trudeau, J., Bombardier, C., Carmona, L., Heijde, D., Bijlsma, J.W.J., Boumpas, D.T., Canhao, H., Edwards, C.J., Hamuryudan, V., Kvien, T.K., Leeb, B.F., Martin-Mola, E.M., Mielants, H., Muller-Ladner, U., Murphy, G., Ostergaard, M., Pereira, I.A., Ramos-Remus, C., Valentini, G., Zochling, J., Dougados, M.: Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3e initiative. Annals of the Rheumatic Diseases **68**(7), 1086–1093 (2008) https://doi.org/10.1136/ard.2008.094474

[117] FUKUSHIMA, R., KANAMORI, S., HIRASHIBA, M., HISHIKAWA, A., MURANAKA, R., KANETO, M., NAKAMURA, K., KATO, I.: Teratogenicity study of the dihydroorotatedehydrogenase inhibitor and protein tyrosine kinase inhibitor leflunomide in mice. Reproductive Toxicology **24**(3–4), 310–316 (2007) https://doi.org/10.1016/j.reprotox.2007.05.006

[118] Chambers, C.D., Johnson, D.L., Robinson, L.K., Braddock, S.R., Xu, R., Lopez-Jimenez, J., Mirrasoul, N., Salas, E., Luo, Y.J., Jin, S., Jones, K.L.: Birth outcomes in women who have taken leflunomide during pregnancy. Arthritis amp;amp; Rheumatism **62**(5), 1494–1503 (2010) https://doi.org/10.1002/art.27358

[119] Cassina, M., Johnson, D.L., Robinson, L.K., Braddock, S.R., Xu, R., Jimenez, J.L., Mirrasoul, N., Salas, E., Luo, Y.J., Jones, K.L., Chambers, C.D.: Pregnancy outcome in women exposed to leflunomide before or during pregnancy. Arthritis amp;amp; Rheumatism **64**(7), 2085–2094 (2012) https://doi.org/10.1002/art.34419

[120] Brent, R.L.: Teratogen update: Reproductive risks of leflunomide (arava?); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. Teratology **63**(2), 106–112 (2001) https: //doi.org/10.1002/1096-9926(200102)63:2<106::aid-tera1017>3.0.co;2-r

[121] Alcorn, N., Saunders, S., Madhok, R.: Benefit-risk assessment of leflunomide: An appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. Drug Safety **32**(12), 1123–1134 (2009) https://doi.org/10.2165/11316650-000000000-00000

[122] Mahadevan, U., Wolf, D.C., Dubinsky, M., Cortot, A., Lee, S.D., Siegel, C.A., Ullman, T., Glover, S., Valentine, J.F., Rubin, D.T., Miller, J., Abreu, M.T.: Placental transfer of anti–tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. Clinical Gastroenterology and Hepatology **11**(3), 286–292 (2013) https://doi.org/10.1016/j.cgh.2012.11.011

[123] Krause, M.L., Amin, S., Makol, A.: Use of dmards and biologics during pregnancy and lactation in rheumatoid arthritis: what the rheumatologist needs to know. Therapeutic Advances in Musculoskeletal Disease **6**(5), 169–184 (2014) https://doi.org/10.1177/1759720x14551568

[124] Carter, J.D., Valeriano, J., Vasey, F.B.: Tumor necrosis factor-alpha inhibition and VATER

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

association: a causal relationship. J. Rheumatol. **33**(5), 1014–1017 (2006)

[125] CARTER, J.D., LADHANI, A., RICCA, L.R., VALERIANO, J., VASEY, F.B.: A safety assessment of tumor necrosis factor antagonists during pregnancy: A review of the food and drug administration database. The Journal of Rheumatology **36**(3), 635–641 (2009) https://doi.org/10.3899/jrheum. 080545

[126] Verstappen, S.M.M., King, Y., Watson, K.D., Symmons, D.P.M., Hyrich, K.L.: Anti-tnf therapies and pregnancy: outcome of 130 pregnancies in the british society for rheumatology biologics register. Annals of the Rheumatic Diseases **70**(5), 823–826 (2011) https://doi.org/10.1136/ard.2010.140822

[127] Diav-Citrin, O., Otcheretianski-Volodarsky, A., Shechtman, S., Ornoy, A.: Pregnancy outcome following gestational exposure to tnf-alpha-inhibitors: A prospective, comparative, observational study. Reproductive Toxicology **43**, 78–84 (2014) https://doi.org/10.1016/j.reprotox.2013.11.004

[128] Mahadevan, U., Martin, C., Sandler, R., Kane, S., Dubinsky, M., Lewis, J., Sandborn, W., Sands, B.: 865 piano: A 1000 patient prospective registry of pregnancy outcomes in women with ibd exposed to immunomodulators and biologic therapy. Gastroenterology **142**, 149 (2012) https:// doi.org/10.1016/S0016-5085(12)60561-7

[129] Lichtenstein, G.R., Feagan, B.G., Cohen, R.D., Salzberg, B.A., Diamond, R.H., Price, S., Langholff, W., Londhe, A., Sandborn, W.J.: Serious infection and mortality in patients with crohn's disease:

More than 5 years of follow-up in the treat™ registry. American Journal of Gastroenterology **107**(9), 1409–1422 (2012) https://doi.org/10.1038/ajg.2012.218

[130] Chambers C, J.K.O.C.R.G. Johnson D: Pregnancy outcome in women exposed to anti-tnf-alpha medications: the otis rheumatoid arthritis in pregnancy study. Arthritis Rheumatol. **50**(9), 1479 (2004)

[131] Katz, J.A., Antoni, C., Keenan, G.F., Smith, D.E., Jacobs, S.J., Lichtenstein, G.R.: Outcome of pregnancy in women receiving infliximab for the treatment of crohn's disease and rheumatoid arthritis. The American Journal of Gastroenterology **99**(12), 2385–2392 (2004) https://doi.org/10. 1111/j.1572-0241.2004.30186.x

[132] Vinet, E., Pineau, C., Gordon, C., Clarke, A.E., Bernatsky, S.: Biologic therapy and pregnancy outcomes in women with rheumatic diseases. Arthritis Care amp;amp; Research **61**(5), 587–592 (2009) https://doi.org/10.1002/art.24462

[133] Nielsen, O.H., Loftus Jr, E.V., Jess, T.: Safety of tnf- inhibitors during ibd pregnancy: a systematic review. BMC Medicine **11**(1) (2013) https://doi.org/10.1186/1741-7015-11-174

[134] Marchioni, R.M.: Tumor necrosis factor-inhibitor therapy and fetal risk: A systematic literature review. World Journal of Gastroenterology **19**(17), 2591 (2013) https://doi.org/10.3748/wjg.v19. i17.2591

[135] Gisbert, J.P., Chaparro, M.: Safety of anti-tnf agents during pregnancy and breastfeeding in women with inflammatory bowel disease. American Journal of Gastroenterology **108**(9), 1426–1438 (2013) https://doi.org/10.1038/ajg.2013.171

[136] Weber-Schoendorfer, C., Oppermann, M., Wacker, E., Bernard, N., Beghin, D., CuppersMaarschalkerweerd, B., Richardson, J.L., Rothuizen, L.E., Pistelli, A., Malm, H., Eleftheriou, G., Kennedy, D., Kadioglu Duman, M., Meister, R., Schaefer, C.: Pregnancy outcome after tnfinhibitor therapy during the first trimester: a prospective multicentre cohort study. British Journal of Clinical Pharmacology **80**(4), 727–739 (2015) https://doi.org/10.1111/bcp.12642

[137] Simister, N.: Placental transport of immunoglobulin g. Vaccine **21**(24), 3365–3369 (2003) https: //doi.org/10.1016/s0264-410x(03)00334-7

[138] Fechtenbaum M, E.P. Md Yusof MY: Certolizumab pegol in rheumatoid arthritis: current update. Expert Opin Biol Ther **14**, 841–891 (2014)

[139] Cheent, K., Nolan, J., Shariq, S., Kiho, L., Pal, A., Arnold, J.: Case report: Fatal case of disseminated bcg infection in an infant born to a mother taking infliximab for crohn's disease. Journal of Crohn's and Colitis **4**(5), 603–605

(2010) https://doi.org/10.1016/j.crohns.2010.05.001

[140] Chakravarty, E.F., Murray, E.R., Kelman, A., Farmer, P.: Pregnancy outcomes after maternal exposure to rituximab. Blood **117**(5), 1499–1506 (2011) https://doi.org/10.1182/blood-2010-07-295444

[141] Sangle, S.R., Lutalo, P.M.K., Davies, R.J., Khamashta, M.A., D'Cruz, D.P.: B-cell depletion therapy and pregnancy outcome in severe, refractory systemic autoimmune diseases. Journal of Autoimmunity **43**, 55–59 (2013) https://doi.org/10.1016/j.jaut.2013.03.001

[142] Pendergraft, W.F., McGrath, M.M., Murphy, A.P., Murphy, P., Laliberte, K.A., Greene, M.F., Niles, J.L.: Fetal outcomes after rituximab exposure in women with autoimmune vasculitis. Annals of the Rheumatic Diseases **72**(12), 2051–2053 (2013) https://doi.org/10.1136/annrheumdis-2013-203833

[143] Fischer-Betz, R.E., Schneider, M.: Biologika in schwangerschaft und stillzeit. Zeitschrift f"ur Rheumatologie **69**(9), 780–787 (2010) https://doi.org/10.1007/s00393-010-0640-2

[144] Kumar, M., Ray, L., Vemuri, S., Simon, T.A.: Pregnancy outcomes following exposure to abatacept during pregnancy. Seminars in Arthritis and Rheumatism **45**(3), 351–356 (2015) https://doi.org/ 10.1016/j.semarthrit.2015.06.016

[145] Pham, T., Bachelez, H., Berthelot, J.-M., Blacher, J., Claudepierre, P., Constantin, A., Fautrel, B., Gaujoux-Viala, C., Go¨eb, V., Gossec, L., Goupille, P., Guillaume-Czitrom, S., Hachulla, E., Lequerr´e, T., Marolleau, J.-P., Martinez, V., Masson, C., Mouthon, L., Pu´echal, X., Richette, P., Saraux, A., Schaeverbeke, T., Soubrier, M., Viguier, M., Vittecoq, O., Wendling, D., Mariette, X., Sibilia, J.: Abatacept therapy and safety management. Joint Bone Spine **79**, 3–84 (2012) https://doi.org/10.1016/s1297-319x(12)70011-8

[146] Anakinra [package insert]. 2013. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/anakam

[147] Chang, Z., Spong, C.Y., Jesus, A.A., Davis, M.A., Plass, N., Stone, D.L., Chapelle, D., Hoffmann, P., Kastner, D.L., Barron, K., Goldbach-Mansky, R.T., Stratton, P.: Brief report: Anakinra use during pregnancy in patients with cryopyrin-associated periodic syndromes. Arthritis amp; Rheumatology **66**(11), 3227–3232 (2014) https://doi.org/10.1002/art.38811

[148] Fischer-Betz, R., Specker, C., Schneider, M.: Successful outcome of two pregnancies in patients with adult-onset still's disease treated with IL-1 receptor antagonist (anakinra). Clin. Exp. Rheumatol. **29**(6), 1021–1023 (2011)

[149] Berger, C.T., Recher, M., Steiner, U., Hauser, T.M.: A patient's wish: anakinra in pregnancy. Ann. Rheum. Dis. **68**(11), 1794–1795 (2009)

[150] Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125276lbl.pdf

[151] Rubbert-Roth A, M.S.H.A. Goupille PM: First experiences with pregnancies in ra patients (pts) receiving tocilizumab (tcz) therapy. Arthritis Rheum. **62**(10), 384 (2010)

[152] Ishikawa HH, K.A.e.a. Kaneko Y: Pregnancy in patients with rheumatoid arthritis treated with biological agents: results of the 8-year of japanese tbc registry. Ann Rheum Dis **71**, 501 (2010)

[153] Nakajima, K., Watanabe, O., Mochizuki, M., Nakasone, A., Ishizuka, N., Murashima, A.: Pregnancy outcomes after exposure to tocilizumab: A retrospective analysis of 61 patients in japan. Modern Rheumatology **26**(5), 667–671 (2016) https://doi.org/10.3109/14397595.2016.1147405

[154] Pham, T., Claudepierre, P., Constantin, A., Bandt, M., Fautrel, B., Gossec, L., Gottenberg, J.-E., Goupille, P., Guillaume, S., Hachulla, E., Masson, C., Morel, J., Pu´echal, X., Saraux, A., Schaeverbeke, T., Wendling, D., Bruckert, E., Pol, S., Mariette, X., Sibilia, J.: Tocilizumab: Therapy and safety management. Joint Bone Spine **77**, 3–100 (2010) https://doi.org/10.1016/s1297-319x(10) 70001-4

[155] Available from: http://www.xeljanz.com/

9 Additional Resources

1. Hydroxychloroquine Prescription Insert http://products.sanofi.ca/en/plaquenil. pdf
2. Sulfasalazine Prescription Insert http://labeling.pfizer.com/ShowLabeling. aspx?id=524

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1725-1746 | ISSN:2251-6727

3. Azathioprine Prescription Insert http://www.tritonpharma.ca/uploads/files/pdf/ imuran-tablet-en.pdf
4. Methotrexate Prescription Insert http://www.rheumatrex.info/pdf/ RheumatrexPackageInsert.pdf
5. Leflunomide Prescription Insert http://prod- ucts.sanofi.us/arava/arava.html
6. Adalimumab Prescription Insert http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/Therapeutic BiologicApplications/ucm092762.pdf
7. Certolizumab Prescription Insert http://www.cimzia.com/pdf/prescribinginformation.pdf
8. Etanercept Prescription Insert http://www.accessdata.fda.gov/drugsatfdadocs/label/2003/etanimm06 0503LB.pdf
9. Golimumab Prescription Insert http://www.simponi.com/shared/product/simponi/prescribinginformation.pdf
10. Infliximab Prescription Insert http://www.remicade.com/ shared/product/remicade/prescribinginformation.pdf
11. Rituximab Prescription Insert http://www. gene.com/download/pdf/rituxanprescribing. pdf
12. Abatacept Prescription Insert http://packageinserts.bms.com/pi/piorencia.pdf
13. Anakinra Prescription Insert http://www.accessdata.fda. gov/drugsatfdadocs/label/2003/anakamg062703 LB.pdf
14. Tocilizumab Prescription Insert http://www.accessdata.fda.gov/drugsatfda docs/label/2010/125276lbl.pdf
15. Tofacitinib Prescription Insert http://www.xel-janz.com/