Reumatizam 2023;70(1):34–48
https://doi.org/10.33004/reumatizam-70-1-5

REVIEW PAPER PREGLEDNI RAD

IMMUNOMODULATORY ANTIRHEUMATIC DRUGS AND NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN PRE-CONCEPTION, PREGNANCY AND BREASTFEEDING – A REVIEW OF THE GUIDELINES

IMUNOMODULATORNA REUMATOLOŠKA TERAPIJA I NESTEROIDNI ANTIREUMATICI PRIJE ZAČEĆA, U TRUDNOĆI I DOJENJU – PREGLED SMJERNICA

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Received / Primljeno: 18th May 2023 / 18. 5. 2023.
Accepted / Prihvaćeno: 16th June 2023 / 16. 6. 2023.

Abstract

The course and outcome of pregnancy can be affected by the activity of the inflammatory rheumatic disease itself and by the drugs we use. Evidence on the safe use of drugs during pregnancy is largely lacking due to the observational nature of the studies conducted and the difficulty of conducting clinical trials in pregnancy. The current guidelines of the professional and scientific societies of rheumatology — the European Alliance of Associations for Rheumatology (EULAR), the American College of Rheumatology (ACR) and the British Society for Rheumatology (BSR) are analysed and consolidated in this review paper. Drugs like methotrexate, leflunomide, mycophenolate mofetil, cyclophosphamide and Janus kinase inhibitors (JAK inhibitors) are contraindicated in pregnancy and should be avoided during pregnancy planning and replaced by drugs that are compatible with pregnancy. Immunomodulators that are considered compatible with pregnancy are prednisone, hydroxychloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, colchicine, dapsone and most biologic drugs. When it comes to biologics, tumour necrosis factor inhibitors (TNF-inhibitors) are the most studied drugs and all of them are safe to use in the first and second trimesters of pregnancy. Certolizumab is considered to be the safest due to almost no placental transfer. There is still insufficient evidence for other biologic drugs, and it is recommended to discontinue them before pregnancy/when pregnancy is confirmed. The use of all biologic drugs can be continued throughout the pregnancy if they are necessary to establish control over the activity of the mother's severe/life-threatening disease. Effective drug treatment of an active inflammatory rheumatic disease is possible with reasonable safety for the mother and the foetus/child during pregnancy and lactation nowadays.

Key words: rheumatic disease, pregnancy, breastfeeding, glucocorticoids, DMARDs, biologics

Sažetak

Upalne reumatske bolesti na različite načine mogu utjecati na tijek i ishod trudnoće, kako zbog aktivnosti same bolesti, tako i zbog lijekova koje primjenjujemo. Dokazi o sigurnoj upotrebi lijekova tijekom trudnoće uglavnom su manjkavi zbog opservacijske prirode studija i poteškoća u provođenju kliničkih ispitivanja u trudnoći. U ovom preglednom radu analizirane su i objedinjene aktualne smjernice reumatoloških stručnih društava – European Alliance of Associations for Rheumatology (EULAR), American College of *Rheumatology (ACR)* i British Society for *Rheumatology* (*BSR*). Metotreksat, leflunomid, mofetilmikofenolat, ciklofosfamid i inhibitori janus kinaze (JAK-inhibitori) kontraindicirani su u trudnoći te ih treba kod planiranja trudnoće isključiti i zamijeniti kompatibilnim lijekom.

Imunomodulatorni lijekovi koji se smatraju kompatibilnima s trudnoćom jesu prednizon, hidroksiklorokin, sulfasalazin, azatioprin, ciklosporin, takrolimus, kolhicin, dapson te većina bioloških lijekova. Inhibitori faktora tumorske nekroze (TNF inhibitori) najbolje su proučeni i svi se smatraju sigurnima u prvom i drugom tromjesečju trudnoće, a certolizumab se smatra najsigurnijim i gotovo bez placentalnog prijenosa kroz sva tri tromjesečja. Za ostale biološke lijekove još uvijek nema dovoljno dokaza i preporučuje ih se prekinuti prije/kod potvrđene trudnoće. Svi biološki lijekovi mogu se nastaviti uzimati kroz čitavu trudnoću ako su potrebni za kontrolu aktivnosti teške/životno ugrožavajuće bolesti majke. Aktivnu upalnu reumatsku bolest danas je uglavnom moguće učinkovito liječiti uz razumnu sigurnost za majku i za plod/dijete tijekom trudnoće i dojenja.

Ključne riječi: reumatske bolesti, trudnoća, dojenje, glukokortikoidi, DMARD-ovi, biološki lijekovi

INTRODUCTION

The course and outcome of pregnancy can be affected by the activity of the inflammatory rheumatic disease itself and by the drugs we use. Therapeutic progress in the treatment of inflammatory rheumatic diseases has led to the widespread use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) with different mechanisms of action, including their biosimilar versions, as well as a new class of targeted synthetic DMARDs (tsDMARDs). There is an increasing number of publications on the use of DMARDs in pregnancy, but the development of new drugs is inevitably accompanied by uncertainty about their use in pregnancy, which can lead to unnecessary medication discontinuation. Medication discontinuation before or during early pregnancy potentially increases the risk of disease activity and exacerbation during pregnancy, so it is extremely important to weigh the potential benefit to the foetus against the risk of loss of disease control before making a decision to choose or change therapy.

The aim of this review is to analyse and consolidate the current guidelines of international and some national professional societies of rheumatology: the EULAR (the European Alliance of Associations for Rheumatology), the *BCR (the* British Society for *Rheumatology*) and the ACR (the American College of R*heumatology)* (1–3) and provide updated information in one place on the compatibility of the most commonly prescribed immunomodulators and non-steroidal anti-inflammatory drugs (NSAIDs) in patients with immune-mediated inflammatory rheumatic diseases during conception, pregnancy and breastfeeding.

According to the latest British, American and European guidelines, the general recommendations for prescribing immunomodulators and NSAIDs in pregnancy are as follows:

1. It is recommended to consult with your physician in the period pre-conception with the aim of optimising the control of rheumatic disease before pregnancy, the timing of pregnancy and medications to be used before/during/after pregnancy, including contraception.
2. The risks and benefits of prescribed medications for the mother as well as the child should be explained thoroughly and clearly documented.

UVOD

Upalne reumatske bolesti na različite načine mogu utjecati na tijek i ishod trudnoće, kako zbog aktivnosti same bolesti, tako i zbog lijekova koje primjenjujemo. Terapijski napredak u liječenju upalnih reumatskih bolesti doveo je do ekspanzije bioloških lijekova koji modificiraju tijek bolesti (bDMARD) različitih mehanizama djelovanja, uključivo i njihove biosličnе inačice, kao i nove klase ciljanih sintetičkih DMARD-ova (tsDMARD). Sve je veći broj publikacija o upotrebi DMARD-ova u trudnoći, ali pojava novih lijekova neminovno je praćena nesigurnošću oko upotrebe u trudnoći, što može dovesti do nepotrebnog prekidanja liječenja. Prekid liječenja prije ili tijekom rane trudnoće potencijalno povisuje rizik od aktivnosti bolesti i pogoršanja tijekom trudnoće, stoga je iznimno važno odvagnuti potencijalnu korist za plod u odnosu na rizik gubitka kontrole bolesti prije nego što donesemo odluku o izboru ili promjeni terapije.

Svrha je ovoga preglednog rada analizirati i objediniti aktualne smjernice međunarodnih i nekih nacionalnih stručnih društava, EULAR-a (European Alliance of Associations for Rheumatology), *BCR-a (*British Society for *Rheumatology*) i ACR-a (American College of R*heumatology)* (1–3), te na jednom mjestu pružiti ažurirane informacije o kompatibilnosti najčešće propisivanih imunomodulatornih lijekova i nesteroidnih antireumatika (NSAR) u bolesnica s imunološki posredovanim upalnim reumatskim bolestima sa začećem, trudnoćom i dojenjem.

Prema najnovijim britanskim, američkim i europskim smjernicama opće preporuke za propisivanje imunomodulatornih lijekova i NSAR-a u trudnoći jesu slijedeće:

1. Preporučuje se savjetovanje prije začeća s ciljem optimizacije kontrole reumatološke bolesti prije trudnoće, izbora vremena trudnoće i izbora lijekova prije/za vrijeme/nakon trudnoće, uključujući i kontracepciju.
2. Rizici i korist propisanih lijekova za majku i dijete trebaju biti komentirani i jasno dokumentirani.
3. Lijekovi koji su kontraindicirani u trudnoći trebaju biti zamijenjeni kompatibilnim lijekovima i to po mogućnosti prije začeća kako bi se utvrdila dobra kontrola bolesti novim lijekom.

3. Drugs that are contraindicated in pregnancy should be replaced by drugs that are compatible with pregnancy, preferably in the period pre-conception in order to establish the control of the disease with the new drug.
4. If there is no suitable drug that would be compatible with pregnancy, the control of the mother's severe/life-threatening disease activity should take precedence over concern for potential foetal outcomes.
5. The use of all biologic drugs can be continued throughout the pregnancy if they are necessary to establish control over the activity of the mother's severe/life-threatening disease.
6. The immunisation schedule of a newborn/infant after in utero exposure to a biologic drug depends on the time of exposure, bioavailability and the mechanism of action of the drug.
7. When the mother's disease is well controlled, the minimum effective dose of the immunomodulator should be used, and medication discontinuation should be considered in cases where there is a low risk of disease exacerbation.
8. Some drugs can reduce male fertility, but paternal exposure has not been linked to the foetal development or adverse pregnancy outcomes (1–3)

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Due to their analgesic and anti-inflammatory activity, non-selective non-steroidal anti-rheumatic drugs (NSAIDs) and selective cyclooxygenase-2 inhibitors (COX-2 inhibitors) are used in a number of inflammatory rheumatic diseases, and they have a special role in the medical treatment of spondyloarthritis, osteoarthritis and gout.

Non-selective NSAIDs and COX-2 inhibitors are associated with an increased risk of unruptured follicle syndrome, which is why it is recommended to avoid them in case of reduced female fertility (2, 4). It is worth noting that a higher risk was found in patients with inactive rheumatic disease and that the risk of this reversible syndrome is higher with the use of COX-2 inhibitors (etoricoxib) than with non-selective NSAIDs (5). Large retrospective studies have conflicting conclusions about the safety of non-selective NSAIDs in the first trimester (5). The EULAR considers that non-selective NSAIDs are compatible with pregnancy in the first and second trimester (3). Considering that certain studies have found an increased risk for spontaneous abortion and malformations (6–8), the BCR recommends that non-selective NSAIDs be used only intermittently in the first and second trimester (4) and the ACR also considers them to be conditionally compatible with pregnancy (2). After the 30th week of

4. Ako nema pogodnog lijeka kompatibilnog s trudnoćom, kontrola aktivnosti teške/životno ugrožavajuće bolesti majke treba imati prednost pred brigom za potencijalne fetalne ishode.
5. Svi biološki lijekovi mogu se nastaviti kroz čitavu trudnoću ako su potrebni za kontrolu aktivnosti teške/životno ugrožavajuće bolesti majke.
6. Kalendar cijepljenja novorođenčeta/dojenčeta nakon *in utero* ekspozicije biološkom lijeku ovisi o vremenu ekspozicije, bioraspoloživosti i mehanizmu djelovanja lijeka.
7. Kada je majčina bolest dobro kontrolirana treba upotrijebiti minimalnu učinkovitu dozu imunomodulatornog lijeka te razmotriti prekid terapije kod niskog rizika od pogoršanja bolesti.
8. Neki lijekovi mogu smanjiti plodnost muškaraca, ali se ekspozicija očeva ne dovodi u vezu s razvojem ploda ili lošim ishodima trudnoće. (1–3)

NESTEROIDNI ANTIREUMATICI

Neselektivni nesteroidni antireumatici (NSAR) i selektivni inhibitori ciklooksigenaze-2 (COX-2 inhibitori) zbog svoje analgetske i protuupalne aktivnosti koriste se kod niza upalnih reumatskih bolesti, a posebno mjesto zauzimaju u medikamentoznom liječenju spondiloartritisa, osteoartritisa i gihta.

Neselektivni NSAR i COX-2 inhibitori dovode se u vezu s povećanim rizikom sindroma nerupturiranog folikula, zbog čega ih se u slučaju smanjene plodnosti žena preporučuje izbjegavati (2, 4). Zanimljivo je da je nađen viši rizik kod bolesnica s inaktivnom reumatskom bolesti i da je rizik ovoga reverzibilnog sindroma viši kod upotrebe COX-2 inhibitora (etorikoksib) nego kod neselektivnih NSAR-a (5). Velike retrospektivne studije imaju oprečne zaključke o sigurnosti neselektivnih NSAR-a u prvom tromjesečju (5). EULAR smatra neselektivne NSAR kompatibilnima s prvim i drugim tromjesečjem (3). Kako su određene studije našle povišeni rizik za spontani pobačaj i malformacije (6–8), BCR preporučuje neselektivne NSAR u prvom i drugom tromjesečju koristiti samo intermitentno (4), a ACR ih također smatra uvjetno kompatibilnima (2). Nakon 30. tjedna trudnoće neselektivne NSAR preporučuje se u potpunosti obustaviti zbog rizika prijevremenog zatvaranja duktusa arteriozusa (2–4). Preporuka FDA (United States Food and Drug Administration) iz 2020. godine jest izbjegavati sve neselektivne NSAR već od 20. tjedna trudnoće umjesto ranije preporučenog 30. tjedna. Ova preporuka donesena je temeljem podataka o povišenom riziku oligohidramniona i bubrežnog oštećenja od 20. tjedna trudnoće (4). COX-2 inhibitore preporučuje se izbjegavati zbog ograničenih podataka o njihovoj upotrebi u trudnoći (2–4). Neselektivni NSAR, posebno ibuprofen, kompa-

pregnancy, non-selective NSAIDs are recommended to be completely discontinued due to the risk of premature closure of the ductus arteriosus (2–4). The FDA (the U.S. Food and Drug Administration) recommendation from 2020 is to avoid all non-selective NSAIDs from the 20th week of pregnancy instead of the previously recommended 30th week. This recommendation was made based on the data on the increased risk of oligohydramnios and kidney damage from the 20th week of pregnancy (4). COX-2 inhibitors are recommended to be avoided due to limited data on their use in pregnancy (2–4). Non-selective NSAIDs, especially ibuprofen, are compatible with breastfeeding (2, 4). Among COX-2 inhibitors, the EULAR highlights the importance of celecoxib, for which there is evidence that corroborates the claim that it is compatible with breastfeeding (9), while other COX-2 inhibitors are not recommended for use during breastfeeding (2–4).

GLUCOCORTICOIDS

Glucocorticoids that are most often used in the treatment of rheumatic diseases (prednisone, methylprednisolone) are metabolised in the placenta, so less than 10% of the active drug reaches the foetus (10). Prednisone and methylprednisolone are compatible with pregnancy with mandatory monitoring of blood pressure and blood glucose. Whenever possible, the dose of prednisone should be less than 20 mg/day, i.e. the lowest dose necessary to establish control over the mother's disease. Prednisone and methylprednisolone are compatible with breastfeeding. After the use of prednisone in a dose of > 20 mg, it is recommended to delay breastfeeding for 4 hours (1–3).

Fluorinated glucocorticoids (dexamethasone, betamethasone) cross the placenta unhindered and are used in the prevention and treatment of premature foetal respiratory distress or congenital heart block.

Intra-articular and intramuscular injections can be safely administered throughout pregnancy (3).

SYNTHETIC ANTIMALARIALS

Due to its immunomodulatory effect, hydroxychloroquine is most often used in the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The dose of hydroxychloroquine used in rheumatic diseases is ≤ 400 mg/day, and it is the DMARD of choice for women who are in the course of pregnancy planning. Based on numerous studies and reports in which no effect on the duration of pregnancy and birth weight, as well as no increased risk or specific pattern of congenital malformations were found, it was noted that hydroxychloroquine is considered compatible with pregnancy at a dose of ≤ 400 mg/day. Hydroxychloroquine is compatible with breastfeeding (1, 2). There are no recommendations regarding the tibilni su s dojenjem (2,4). EULAR među COX-2 inhibitorima ističe celekoksib za koji postoje dokazi o kompatibilnosti (9), dok se ostale ne preporučuje u dojenju (2–4).

GLUKOKORTIKOIDI

Glukokortikoidi koji se najčešće koriste u liječenju reumatskih bolesti (prednizon, metilprednizolon) metaboliziraju se u placenti, tako da manje od 10% aktivnog lijeka dođe do ploda (10). Prednizon i metilprednizolon su kompatibilni s trudnoćom uz obvezno praćenje arterijskog tlaka i glukoze u krvi. Kad je to moguće doza prednizona treba biti manja od 20 mg/dan, odnosno najniža potrebna za kontrolu bolesti majke. Prednizon i metilprednizolon su kompatibilni s dojenjem. Nakon doze prednizona > 20 mg preporučuje se odgoditi dojenje za četiri sata (1–3).

Fluorirani glukokortikoidi (deksametazon, betametazon) neometano prolaze placentu te se koriste u prevenciji i liječenju npr. fetalnoga respiratornog distresa ili kongenitalnoga srčanog bloka.

Intraartikularne i intramuskularne injekcije mogu se sigurno aplicirati kroz čitavu trudnoću (3).

SINTETSKI ANTIMALARICI

Hidroksiklorokin se zbog svoga imunomodulatornog učinka najčešće koristi u liječenju reumatoidnog artritisa (RA) i sistemskoga eritemskog lupusa (SLE). Doza hidroksiklorokina koja se koristi u reumatskim bolestima jest ≤ 400 mg/dan i DMARD je izbora kod žena koje planiraju trudnoću. Temeljem brojnih studija i izvještaja u kojima nije nađen utjecaj na trajanje trudnoće i porođajnu težinu, kao ni povećan rizik ili specifičan obrazac kongenitalnih malformacija, hidroksiklorokin se smatra sigurnim u trudnoći u dozi ≤ 400 mg/dan. Hidroksiklorokin je kompatibilan s dojenjem (1,2). Vezano za upotrebu klorokina u trudnoći/dojenju ovdje analizirane smjernice ne daju preporuku.

SULFASALAZIN

Sulfasalazin je konvencionalni sintetski DMARD (csDMARD) koji se u reumatologiji koristi u liječenju RA, PsA i drugih seronegativnih artritisa te juvenilnoga idiopatskog artritisa (JIA). Sulfasalazin je kompatibilan s trudnoćom, a dodatna preporuka EULAR-a jest ograničiti dozu na dva grama dnevno (3). Kod propisivanja sulfasalazina preporučuje se prije začeća i kroz prvo tromjesečje trudnoće provoditi suplementaciju folnom kiselinom 5 mg dnevno. Sulfasalazin je kompatibilan s dojenjem zdrave donesene djece (1,2). Dojenje se ne preporučuje kod bolesne djece, kod nedonoščadi, kod hiperbilirubinemije ili deficijencije glukoza-6-fosfat dehidrogenaze (11).

use of chloroquine during pregnancy/breastfeeding in the guidelines analysed in this review.

SULFASALAZINE

Sulfasalazine is a conventional synthetic DMARD (csDMARD) used in rheumatology in the treatment of RA, PsA and other seronegative rheumatoid arthritis and juvenile idiopathic arthritis (JIA). Sulfasalazine is compatible with pregnancy, and the additional recommendation of the EULAR is to limit the dose to 2 g per day (3). When prescribing sulfasalazine, it is important to recommend patients to take it with folic acid in a dose of 5 mg/day in the period pre-conception and throughout the first trimester. Sulfasalazine is compatible with breastfeeding of healthy term infants (1, 2). Breastfeeding is not recommended for sick children, premature infants, in cases of hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency. (11).

AZATHIOPRINE

Azathioprine is an antimetabolite immunosuppressant used in the treatment of numerous inflammatory rheumatic diseases, e.g. SLE, idiopathic inflammatory myopathies (IIM) and systemic vasculitis. Azathioprine is compatible with pregnancy. The EULAR recommendation is to limit the dose to 2 mg/kg/day (3). Azathioprine is compatible with breastfeeding, but is considered to be conditionally recommended by the ACR due to the proven low transfer rate into breast milk (1, 2).

COLCHICINE AND DAPSONE

Colchicine is an antimitotic alkaloid with anti-inflammatory activity that is used in the treatment of gout and other autoinflammatory diseases, e.g. familial Mediterranean fever and Behçet's disease. Colchicine in a dose of up to 2 mg per day is compatible with pregnancy (1, 2). The EULAR recommendation is to limit the dose to 1 mg/day (3). Colchicine is compatible with breastfeeding. After the use of colchicine, it is recommended to delay breastfeeding for 2 — 4 hours (4).

Dapsone is a sulfone antibiotic (antileprotic) with anti-inflammatory properties that is used in the treatment of cutaneous lupus erythematosus, neutrophilic dermatoses and certain forms of vasculitis. Dapsone is compatible with pregnancy and breastfeeding. Due to the risk of haemolytic anaemia, regular screening of newborns/infants for signs of haemolysis is recommended (4).

CYCLOSPORINE AND TACROLIMUS

Cyclosporine and tacrolimus are selective calcineurin inhibitors that are most often used in rheumatology for the treatment of SLE.

Cyclosporine and tacrolimus are considered to be compatible by the BSR and the EULAR, while the ACR

AZATIOPRIN

Azatioprin je imunosupresivni antimetabolit koji se koristi u liječenju brojnih upalnih reumatskih bolesti, npr. SLE, idiopatskih inflamatornih miopatija (IIM) i sistemskih vaskulitisa. Azatioprin je kompatibilan s trudnoćom. Preporuka EULAR-a je ograničiti dozu na 2 mg/kg/dan (3). Azatioprin je kompatibilan s dojenjem, s tim da ga ACR smatra uvjetno kompatibilnim zbog dokazanoga manjeg prijelaza u majčino mlijeko (1,2).

KOLHICIN I DAPSON

Kolhicin je antimitotski alkaloid s protuupalnim djelovanjem koji se koristi se u liječenju gihta i drugih autoinflamatornih bolesti, npr. obiteljske mediteranske vrućice i Behçetove bolesti. Kolhicin u dozi do 2 mg dnevno kompatibilan je s trudnoćom (1,2). Preporuka EULAR-a je ograničiti dozu na 1 mg dnevno (3). Kolhicin je kompatibilan s dojenjem. Nakon doze kolhicina preporučuje se odgoditi dojenje za 2 – 4 sata (4).

Dapson je sulfonski antibiotik (antileprotik) s protuupalnim djelovanjem koji se koristi u liječenju kožnog lupusa eritematozusa, neutrofilnih dermatoza i određenih vaskulitisa. Dapson se može koristiti u trudnoći i dojenju. Zbog rizika hemolitičke anemije preporučuju se redoviti kontrolni pregledi (engl. *screening* novorođenčeta/dojenčeta na znakove hemolize (4).

CIKLOSPORIN I TAKROLIMUS

Ciklosporin i takrolimus su selektivni inhibitori kalcineurina koji se u reumatologiji najčešće koriste u liječenju SLE.

Ciklosporin i takrolimus BSR i EULAR smatraju kompatibilnima, dok ih ACR smatra uvjetno kompatibilnima s trudnoćom i dojenjem. Zbog većeg rizika za arterijsku hipertenziju, preeklampsiju i gestacijski dijabetes preporučuje se redovita kontrola arterijskog tlaka, ureje, kreatinina, glukoze, kao i koncentracije lijeka za vrijeme trudnoće. Ciklosporin i takrolimus u malim količinama mogu prijeći u majčino mlijeko i iako nisu dokazani u krvi dojenčeta i nisu zabilježeni štetni učinci ACR ih smatra uvjetno kompatibilnima s dojenjem (1–3).

METOTREKSAT

Metotreksat je csDMARD koji se koristi u liječenju brojnih upalnih reumatskih bolesti i zlatni je standard u liječenju RA. Metotreksat je teratogen i kontraindiciran je u trudnoći i dojenju u svim dozama. Savjetuje se prekinuti uzimanje metotreksata 1 – 3 mjeseca prije planirane trudnoće. U slučaju izloženosti metotreksatu u maloj dozi (≤ 25 mg/tjedan) unutar mjesec dana prije začeća preporučuje se uvesti folnu kiselinu 5 mg dnevno do 12. tjedna trudnoće. Kod neplanirane trud-

considers them conditionally compatible during pregnancy and breastfeeding. Due to the higher risk of arterial hypertension, preeclampsia and gestational diabetes, regular monitoring of arterial pressure, urea, creatinine, glucose and drug concentration during pregnancy is recommended. Cyclosporine and tacrolimus can transfer into breast milk in small amounts and, although they have not been detected in the blood concentration of breastfed infants and no adverse effects have been reported, the ACR considers them conditionally recommended during breastfeeding (1–3).

METHOTREXATE

Methotrexate is a csDMARD used in the treatment of numerous inflammatory rheumatic diseases and it is the gold standard in the treatment of RA. Methotrexate has teratogenic effects and is contraindicated in pregnancy and breastfeeding in all doses. It is advised to discontinue methotrexate 1 — 3 months before the planned pregnancy. In case of exposure to methotrexate in a low dose (≤ 25 mg/week) within a month in the period pre-conception, patients are advised to take folic acid in a dose of 5 mg/day until the 12th week of pregnancy. In case of an unplanned pregnancy on a low dose of methotrexate (≤ 25 mg/week) the risk to the foetus is minimal. It is recommended to discontinue methotrexate immediately, to take folic acid in a dose of 5 mg/day and to be under close monitoring by an obstetrician due to the risk of developing foetal anomalies. Exposure of the foetus to high doses of methotrexate (500 mg/m2) used for cancer treatment represents a high risk for serious malformations and is an indication for induced abortion. A negligible amount of methotrexate is excreted in breast milk, but due to the theoretical risk and insufficient data, it is not recommended to use it during breastfeeding (1–3).

LEFLUNOMIDE

Leflunomide is a csDMARD used in the treatment of RA, PsA and other types of seronegative arthritis.

Leflunomide has not been shown to have teratogenic effects. An analysis of over 700 pregnancies exposed to leflunomide did not show an increased risk for adverse effects (12), but given the fact that there is insufficient evidence that confirms that it is compatible with pregnancy, its use is not recommended before or during pregnancy. It is recommended to discontinue leflunomide 24 months in the period pre-conception or perform a cholestyramine washout (cholestyramine at a dose of 8 g three times a day for 11 days or cholestyramine at a dose of 4 g three times a day if cholestyramine at a dose of 8 g three times a day is not well tolerated). In cases of unplanned pregnancies during which the patients have been taking leflunomide, the patients are recommended to discontinue leflunomide,

noće na maloj dozi metotreksata (≤ 25 mg/tjedan) postoji minimalan rizik za plod. Preporučuje se metotreksat odmah prekinuti, uvesti folnu kiselinu 5 mg dnevno te pažljivo opstetrički pratiti zbog rizika fetalnih anomalija. Izloženost ploda velikim dozama metotreksata (500 mg/m^2) koje se koriste u onkologiji predstavlja velik rizik za ozbiljne malformacije i indikacija je za medicinski uvjetovani pobačaj. U mlijeko se izlučuje zanemariva količina metotreksata, ali se zbog teoretskog rizika i nedovoljno podataka ne preporučuje kod dojenja (1–3).

LEFLUNOMID

Leflunomid je csDMARD koji se koristi u liječenju RA, PsA te drugih seronegativnih artritisa.

Leflunomid nije dokazano teratogen. Analizom više od 700 trudnoća izloženih leflunomidu nije nađen povećani rizik za neželjene događaje (12), ali kako nema dovoljno dokaza o kompatibilnosti s trudnoćom ne preporučuje se prije, niti za vrijeme trudnoće. Preporučuje se prekinuti leflunomid 24 mjeseca prije začeća ili provesti kolestiraminski *washout* (kolestiramin u dozi od 8 g triput na dan tijekom 11 dana ili kolestiramin u dozi od 4 g triput na dan, ako se kolestiramin u dozi od 8 g triput na dan ne podnosi). Pacijenticama na leflunomidu koje neplanirano zatrudne preporučuje se prekinuti leflunomid i provesti kolestiraminski *washout* te ih se upućuje na opstetričko praćenje. Leflunomid nije kompatibilan s dojenjem (1–3).

CIKLOFOSFAMID

Ciklofosfamid je citostatik koji se u reumatologiji koristi u liječenju SLE, skleroderme (SSc), IIM i sistemskih vaskulitisa.

Ciklofosfamid je gonadotoksičan i prije ekspozicije ciklofosfamidu savjetuje se razmotriti neku od metoda očuvanja fertiliteta kao što je krioprezervacija oocita ili primjena agonista hormona koji oslobađa gonadotropine (GnRH) (1).

Ciklofosfamid je dokazano teratogen te je kontraindiciran u trudnoći i dojenju. Ciklofosfamid se savjetuje prekinuti najmanje tri mjeseca prije planirane trudnoće (2). Iznimno se može razmotriti u drugom i trećem tromjesečju trudnoće u slučaju da se radi o teškoj bolesti majke koja joj ugrožava život ili neki organ (1–3).

MOFETILMIKOFENOLAT

Mofetilmikofenolat je imunosupresiv koji se u reumatologiji najčešće koristi u liječenju SLE, SSC, IIM i sistemskih vaskulitisa.

Mofetilmikofenolat je dokazano teratogen i kontraindiciran je u trudnoći i dojenju u bilo kojoj dozi. Kod planiranja trudnoće preporučuje se prekinuti mofetilmikofenolat i zamijeniti ga kompatibilnim lijekom naj-

carry out a cholestyramine washout and be referred for an appointment with an obstetrician for further monitoring. Leflunomide is not compatible with breastfeeding (1–3).

CYCLOPHOSPHAMIDE

Cyclophosphamide is a cytostatic used in rheumatology in the treatment of SLE, scleroderma (SSc), IIM and systemic vasculitis.

Cyclophosphamide has a gonadotoxic effect and before exposure to this drug it is advised to consider one of the fertility preservation procedures such as oocyte cryopreservation or the administration of gonadotropin-releasing hormone (GnRH) agonists (1).

Cyclophosphamide has proven teratogenic effects and is contraindicated in pregnancy and breastfeeding. It is advised to discontinue cyclophosphamide at least three months before a planned pregnancy (2). In exceptional cases, it can be considered in the second and third trimester in case of severe life/organ-threatening illness of the mother (1–3).

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil has a cytostatic effect and it is most commonly used in rheumatology in the treatment of SLE, systemic sclerosis (SSC), IIM and systemic vasculitis.

Mycophenolate mofetil has proven teratogenic effects and it is contraindicated in pregnancy and breastfeeding in any dose. When planning a pregnancy, it is recommended to discontinue mycophenolate mofetil and replace it with a suitable drug at least six weeks in the period pre-conception in order to determine the stability of the disease. In cases of unplanned pregnancies during which the patients have been taking mycophenolate mofetil, the patients are recommended to discontinue mycophenolate mofetil, replace this drug with a drug that is compatible with pregnancy and be referred for an appointment with an obstetrician for close monitoring due to the risk of developing foetal anomalies (1–3).

JAK INHIBITORS

JAK inhibitors are tsDMARDs used in rheumatology in the treatment of RA, PsA, SpA and JIA.

Due to the small size of the molecule and expected placental transfer, as well as passage into milk, JAK inhibitors are not considered to be compatible with pregnancy and breastfeeding. JAK inhibitors have a short half-life (e.g. tofacitinib has a half-life of approximately 3 hours), but their biological effects last longer (e.g. suppression of NK cells lasts for approximately two weeks). In 2016, the EULAR gave a recommendation to discontinue tofacitinib at least two months before the planned pregnancy (3), and in 2022 the BCR recmanje šest tjedana prije začeća kako bi se utvrdila stabilnost bolesti. U slučaju neplanirane trudnoće pod terapijom mofetilmikofenolatom, savjetuje se mofetilmikofenolat ukinuti, uvesti terapiju kompatibilnu s trudnoćom i uputiti na pažljivo opstetričko praćenje zbog rizika fetalnih anomalija (1–3).

JAK-INHIBITORI

JAK-inhibitori su tsDMARD-ovi koji se u reumatologiji koriste u liječenju RA, PsA, SpA i JIA.

Zbog male veličine molekule i očekivanoga placentalnog transfera, kao i prelaska u mlijeko, JAK-inhibitori se ne smatraju kompatibilnima s trudnoćom i dojenjem. JAK-inhibitori imaju kratko vrijeme poluživota (npr. tofacitinib oko tri sata), ali biološki učinci traju duže (pr. supresija NK stanica traje oko dva tjedna). EULAR je 2016. godine dao preporuku da se tofacitinib prekine najmanje dva mjeseca prije planirane trudnoće (3), a BCR 2022. preporučuje JAK-inhibitore prekinuti najmanje dva tjedna prije planirane trudnoće (1).

INTRAVENSKI IMUNOGLOBULINI

Intravenski imunoglobulini, osim kao nadomjesna terapija u imunodeficijencijama, koriste se kao imunomodulatorna terapija u brojnim upalnim reumatskim bolestima. Intravenski imunoglobulini imaju svoje mjesto u liječenju antifosfolipidnog sindroma i imunotrombocitopenije u trudnoći te u prevenciji kongenitalnoga srčanog bloka anti-Ro/La pozitivnih majki. Intravenski imunoglobulini su kompatibilni s trudnoćom i dojenjem (1).

BIOLOŠKI LIJEKOVI

U ranoj trudnoći neznačajne količine IgG-a prenose se pasivnom difuzijom i na kraju prvog tromjesečja u krvi ploda dobivenom kordocentezom mjeri se samo 5–10 % majčine razine IgG-a (13). Aktivni prijenos IgG-a počinje tek između 17. i 22. tjedna trudnoće, kada započinje ekspresija Fc receptora na sinciciotrofloblastu (14). Za aktivni placentalni prijenos potreban je Fc fragment pa se formulacije bez Fc domene (certolizumab pegol) gotovo uopće ne prenose. Većina bioloških lijekova koji se koriste u reumatologiji potpuna su monoklonska protutijela i to subklase IgG1, dok ih je tek nekoliko klase IgG2 i IgG4 (iksekizumab IgG4, eculizumab IgG2/IgG4). Stopa placentalnog prijenosa imunoglobulina ovisi o klasi i subklasi imunoglobulina pa je afinitet za transport IgG1 najveći, a slijede ga IgG4, IgG3 i IgG2 (15).

INHIBITORI TNF-A

Najčešće indikacije za inhibitore TNF-α u reumatologiji jesu RA, PsA, SpA i JIA. Trenutno je registrirano pet inhibitora TNF-α (infliksimab, etanercept, adali-

ommended to discontinue JAK inhibitors at least two weeks before the planned pregnancy (1).

INTRAVENOUS IMMUNOGLOBULINS

Intravenous immunoglobulins are used, in addition to their use as replacement therapy in immunodeficiencies, as immunomodulators for the treatment of numerous inflammatory rheumatic diseases. Intravenous immunoglobulins have an important role in the treatment of antiphospholipid syndrome and immune thrombocytopenia in pregnancy and in the prevention of congenital heart block in mothers who tested positive for anti-Ro/La antibodies. Intravenous immunoglobulins are compatible with pregnancy and breastfeeding (1).

BIOLOGICS

In early pregnancy, insignificant amounts of IgG are transferred by passive diffusion, and at the end of the first trimester, only 5–10% of maternal IgG levels are measured in foetal blood samples obtained by cordocentesis (13). Active transfer of IgG occurs only between the 17th and 22nd week of pregnancy when the expression of the Fc receptor antigens in the syncytiotrophoblast begins (14). An Fc fragment is required for an active placental transfer, so formulations without the Fc domain (certolizumab pegol) have little almost no placental transfer. Most of the biologics used in rheumatology are complete monoclonal antibodies of the IgG1 subclass, while only a few are of the IgG2 and IgG4 classes (ixekizumab, an IgG4 variant, eculizumab an IgG2/IgG4 variant). The rate of placental transfer of immunoglobulin depends on the class and subclass of immunoglobulin, so IgG1 has the highest affinity for transport, followed by IgG4, IgG3 and IgG2 (15).

TNF-ALPHA INHIBITORS

The most common indications for TNF-α inhibitors in rheumatology are RA, PsA, SpA and JIA. Five TNF-α inhibitors are currently approved for clinical use (infliximab, etanercept, adalimumab, certolizumab pegol, golimumab). TNF-α has a role in organogenesis and previously there were some concerns about the risk of its use and the development of congenital abnormalities. However, numerous observational studies and data from registries indicate a good safety profile of TNF-alpha inhibitors without an increased risk of congenital malformations, spontaneous abortions or intrauterine foetal demise (16–18). Transfer of TNF-alpha inhibitors to the foetus can lead to immunosuppression and insufficient immune response to infections and vaccinations (15, 19). It is recommended to postpone live vaccines (BCG, rotavirus vaccine, measles, rubella and mumps vaccine) for 6 to 12 months after exposure to TNF-alpha inhibitors (1–3, 20).

mumab, certolizumab, golimumab). TNF-α ima ulogu u organogenezi i ranije je postojala bojazan od kongenitalnih abnormalnosti. Međutim, brojna opservacijska istraživanja i podatci iz registara ukazuju na dobar sigurnosni profil inhibitora TNF-α bez povišenog rizika kongenitalnih malformacija, spontanih pobačaja ili intrauterine smrti (16–18). Transfer inhibitora TNF-α prema plodu može dovesti do imunosupresije i nedostatnog odgovora na infekcije i cijepljenja (15,19). Preporučuje se odgoditi živa cjepiva (BCG, cjepivo protiv rotavirusa, cjepivo protiv morbila, rubele i parotitisa) za 6 do 12 mjeseci od ekspozicije inhibitorima TNF-α (1–3,20).

Certolizumab je po strukturi fragment protutijela bez Fc domene te stoga bez placentalnog transfera ili s minimalnim placentalnim transferom. Certolizumab je kompatibilan sa sva tri tromjesečja trudnoće i ne zahtijeva nikakve promjene u kalendaru cijepljenja novorođenčeta (21).

Bolesnice bez aktivnosti bolesti ili s niskom aktivnosti bolesti koje su stabilno na inhibitoru TNF-α s poznatim placentalnim transferom (infliksimab, adalimumab, golimumab, etanercept) nije potrebno prije, niti za vrijeme trudnoće prebacivati na certolizumab (1).

Trudnice kod kojih je mala vjerojatnost relapsa bolesti uslijed ukidanja inhibitora TNF-α, trebaju prekinuti: infliksimab u 20. tjednu, adalimumab i golimumab u 28. tjednu i etanercept u 32. tjednu, tako da doneseno novorođenče ima uobičajen kalendar cijepljenja (preporuka BSR-a) (1). EULAR-ova preporuka je slična: prekinuti infliksimab u 20. tjednu, adalimumab u 20. tjednu, etanercept u 30. – 32. tjednu, a za golimumab je 2016. godine bila preporuka prekinuti zbog nedostatka dokaza (3). Preporuka ACR-a je ukinuti infliksimab, adalimumab, golimumab i etanercept u trećem tromjesečju, odnosno nekoliko tjedana prije poroda (2).

Ako je potrebno, infliksimab, adalimumab, golimumab i etanercept mogu se nastaviti kroz čitavu trudnoću kako bi se održala kontrola bolesti. U ovim slučajevima živa cjepiva treba odgoditi za najmanje šest mjeseci od ekspozicije *in utero*. Ako je inhibitor TNF-α pauziran u trudnoći, može se opet uvesti nakon poroda ako nema infektivnih/kirurških komplikacija. Zbog niske stope prijenosa u mlijeko svi inhibitori TNF-α smatraju se kompatibilnima s dojenjem (1–3).

ABATACEPT

Abatacept je selektivni modulator kostimulacije koji se koristi u liječenju RA, PsA i JIA.

Abatacept se preporučuje prekinuti kod začeća/u trudnoći. Nema dokaza o teratogenosti, ali su ograničeni podatci o sigurnosti. U slučaju teške bolesti majke može se razmotriti davanje u trudnoći ako nema drugog kompatibilnog lijeka. U slučaju izloženosti ploda u trećem tromjesečju živa cjepiva treba odgoditi za šest

Certolizumab is structurally an antibody fragment without the Fc domain and therefore it is showing no to minimal placental transfer. Certolizumab is suitable for use during all three trimesters of pregnancy and does not require any adjustments in the immunisation schedule of a newborn (21).

Patients with no disease activity or low disease activity who are maintaining stable treatment with the use of a TNF-alpha inhibitor with proven placental transfer (infliximab, adalimumab, golimumab, etanercept) do not need to replace this drug with certolizumab before or during pregnancy (1).

Pregnant women with a low probability of disease relapse due to discontinuation of TNF-alpha inhibitors should discontinue the following drugs: infliximab at week 20, adalimumab and golimumab at week 28, and etanercept at week 32 so that the newborn has the usual immunisation schedule (the BSR recommendation (1)). The EULAR's recommendation is similar: to discontinue infliximab at week 20, adalimumab at week 20, etanercept at week 30–32, and a 2016 recommendation for golimumab was to discontinue this drug due to lack of evidence (3). The ACR's recommendation is to discontinue infliximab, adalimumab, golimumab and etanercept in the third trimester, i.e. at least a few half-lives before delivery (2).

If necessary, the use of infliximab, adalimumab, golimumab, and etanercept can be continued throughout pregnancy to maintain disease control. In these cases, live vaccines should be postponed for at least six months after exposure in utero. If a TNF-α inhibitor is discontinued during pregnancy, it can be reintroduced after delivery if there are no infectious/surgical complications. Due to their low transfer rate into breast milk, all TNF-α inhibitors are considered to be compatible with breastfeeding (1–3).

ABATACEPT

Abatacept is a selective costimulation modulator used in the treatment of RA, PsA and JIA.

It is recommended to discontinue its use in case of conception/pregnancy. There is no evidence of its teratogenic effect, but there are limited safety data on its use. In case of severe maternal illness, its administration during pregnancy can be considered if there is no other compatible drug. In case of foetal exposure in the third trimester, live vaccines should be postponed for 6 months (1–3). According to the BSR recommendations, abatacept is considered to be compatible with breastfeeding.

IL-6 INHIBITORS

IL-6 inhibitors are used in the treatment of RA, JIA, adult-onset Still's disease (AOSD) and giant cell arteritis (GCA).

mjeseci (1–3). Prema preporukama BSR-a abatacept se smatra kompatibilnim s dojenjem.

INHIBITORI IL-6

Inhibitori IL-6 se koriste u liječenju RA, JIA, Stillove bolesti odrasle dobi (AOSD) i gigantocelularnog arteritisa (GCA).

Tocilizumab se preporučuje prekinuti kod začeća/u trudnoći. Nema dokaza o teratogenosti, ali su ograničeni podatci o sigurnosti. U slučaju teške bolesti majke može se razmotriti davanje u trudnoći ako nema drugog kompatibilnog lijeka. U slučaju izloženosti ploda u trećem tromjesečju živa cjepiva treba odgoditi za šest mjeseci. Prema preporukama BSR-a tocilizumab se smatra kompatibilnim s dojenjem (1).

Za sarilumab su podatci iznimno ograničeni i spominje se samo u preporukama BSR-a. Preporuka BSR-a je ista kao i za tocilizumab (1).

RITUKSIMAB

Rituksimab je anti-CD20 antitijelo koje izaziva B-staničnu depleciju. U reumatologiji je indiciran u RA i vaskulitisima, mikroskopskom poliangiitisu i granulomatozi s poliangiitisom, a osim toga ima najveći broj *off-label* indikacija.

Za rituksimab nema dokaza o teratogenosti, ali ograničeni su podatci o sigurnosti te se preporučuje prekinuti ga prije začeća, odnosno u trudnoći. Starije preporuke su bile prekinuti rituksimab najmanje šest mjeseci prije začeća, ali s obzirom na to da se radi o protutijelu IgG1 čiji aktivni placentarni transport počinje najranije u 16. tjednu trudnoće, BSR i ACR preporučuju da se rituksimab prekine kod začeća (1,2).

Za kontrolu teške bolesti majke može se razmotriti davanje u trudnoći ako nema drugoga kompatibilnog lijeka. Kod izloženosti ploda u trećem tromjesečju postoji rizik B-deplecije te se preporučuje odgoditi živa cjepiva do šestog mjeseca života dojenčeta (1–3). Prema preporukama BCR-a i ACR-a rituksimab se smatra kompatibilnim s dojenjem, a u vrijeme EULAR-ovih smjernica nije bilo dovoljno dokaza.

BELIMUMAB

Belimumab blokirajući djelovanje B-limfocitnog stimulatora (BLyS) smanjuje broj B-limfocita i prvo je monoklonsko protutijelo odobreno za liječenje SLE.

Belimumab se preporučuje prekinuti kod začeća/u trudnoći. Nema dokaza o teratogenosti, ali su ograničeni podaci o sigurnosti. U slučaju teške bolesti majke može se razmotriti davanje u trudnoći ako nema drugog kompatibilnog lijeka. U slučaju izloženosti ploda u trećem tromjesečju živa cjepiva treba odgoditi za šest mjeseci. Prema preporukama BSR-a belimumab se smatra kompatibilnim s dojenjem, a prema ACR-u

It is recommended to discontinue the use of tocilizumab in case of conception/pregnancy. There is no evidence of its teratogenic effect, but there are limited safety data on its use. In case of severe maternal illness, its administration during pregnancy can be considered if there is no other compatible drug. In case of foetal exposure in the third trimester, live vaccines should be postponed for 6 months. According to the BSR recommendations tocilizumab is considered to be compatible with breastfeeding (1).

For sarilumab, the data are extremely limited, and it is only mentioned in the BSR recommendations. The BSR recommendation is the same as for tocilizumab (1).

RITUXIMAB

Rituximab is an anti-CD20 antibody that induces B-cell depletion. In rheumatology, it is indicated in RA and vasculitis, microscopic polyangiitis and granulomatosis with polyangiitis, and it also has the largest number of off-label uses.

There is no evidence of its teratogenic effect, but there are limited safety data on this drug, and it is recommended to discontinue it in the period pre-conception, i.e. during pregnancy. In some of the older recommendations it was stated that rituximab should be discontinued at least six months before conception, but since it is an IgG1 antibody whose active placental transport begins at the 16th week of pregnancy, the BSR and the ACR recommend discontinuing rituximab at conception (1, 2).

In order to maintain control over severe maternal illness, its administration during pregnancy can be considered if there is no other compatible drug. With foetal exposure in the third trimester, there is a risk of B-cell depletion, and it is recommended to postpone live vaccines until the 6th month of the infant's life (1–3). According to the BCR and the ACR recommendations, rituximab is considered to be compatible with breastfeeding, and at the time when the EULAR's guidelines were published, there was no sufficient evidence on this matter.

BELIMUMAB

By blocking the action of the B-lymphocyte stimulator (BLyS), belimumab reduces the number of B lymphocytes and it is the first monoclonal antibody approved for the treatment of SLE.

It is recommended to discontinue the use of belimumab in case of conception/pregnancy. There is no evidence of its teratogenic effect, but there are limited safety data on its use. In case of severe maternal illness, its administration during pregnancy can be considered if there is no other compatible drug. In case of foetal exposure in the third trimester, live vaccines should be postponed for six months. According to the BSR recuvjetno kompatibilnim, dok u vrijeme EULAR-ovih smjernica nije bilo dovoljno dokaza (1, 2).

INHIBITORI IL-1

Inhibitori IL-1 koriste se u liječenju sindroma periodičnih vrućica, Stillove bolesti u dječjoj i odrasloj dobi (sJIA, AOSD) i u uričnom artritisu.

Anakinra je rekombinatni IL-1 receptor antagonist (IL-1Ra) velike molekularne mase koji ne prolazi placentu, dok je kanakinumab humano monoklonsko protutijelo na IL-1 s aktivnim placentarnim transportom od drugog tromjesečja. Nema dokaza o teratogenosti i izloženost inhibitorima IL-1 u trudnoći vjerojatno nije štetna, međutim podatci o sigurnosti su ograničeni. ACR i EULAR daju preporuke samo za anakinru, a BSR zajedničku preporuku za oba inhibitora IL-1. Inhibitore IL-1 preporučuje se prekinuti kod začeća/u trudnoći, ali za kontrolu teške bolesti majke može se razmotriti davanje u trudnoći ako nema drugoga kompatibilnog lijeka (1–3). U slučaju izloženosti ploda u trećem tromjesečju savjetuje se odgoditi živa cjepiva nakon šestog mjeseca života dojenčeta. Prema preporukama BSR-a inhibitori IL-1 se smatraju kompatibilnima s dojenjem. Prema ACR-u anakinra je uvjetno kompatibilna s dojenjem, a u vrijeme EULAR-ovih smjernica nije bilo dovoljno dokaza (1, 2).

INHIBITORI IL-17

Inihibitori IL-17 u reumatologiji se koriste u liječenju SpA, PsA i JIA.

Preporuka BSR je zajednička za oba inhibitora IL-17, sekukinumab i iksekizumab. Za inhibitore IL-17 nema dokaza o teratogenosti, ali su ograničeni podatci o sigurnosti. Inhibitore IL-17 preporučuje se prekinuti kod začeća/u trudnoći. U slučaju teške bolesti majke može se razmotriti davanje u trudnoći ako nema drugoga kompatibilnog lijeka. U slučaju izloženosti ploda u trećem tromjesečju živa cjepiva treba odgoditi do navršenog šestog mjeseca života dojenčeta (1).

ACR za sekukinumab daje istovjetnu preporuku kao i BSR, a za iksekizumab ne daje preporuku (2). EULAR-ove smjernice iz 2016. godine ne komentiraju inhibitore IL-17 jer su u to vrijeme sekukinumab (2015.) i iksekizumab (2016.) tek došli na tržište.

Prema preporukama BSR-a inhibitore IL-17 smatra se kompatibilnima, a prema ACR-u sekukinumab uvjetno kompatibilnim s dojenjem (1, 2).

INHIBITOR IL-12/23

Blokada IL-12/23 u reumatologiji se koristi u liječenju PsA.

Ustekinumab se preporučuje prekinuti kod začeća/u trudnoći. Nema dokaza o teratogenosti, ali su ograničeni podatci o sigurnosti. U slučaju teške bolesti majke

Table 1 Summary of drug compatibility in pregnancy and breastfeeding
Tablica 1. Pregled kompatibilnosti lijekova s trudnoćom i dojenjem

Medicine / Lijek	Pre-conception / Prije začeća	First trimester / Prvo tromjesečje	Second-third trimester / Drugo i treće tromjesečje	Breastfeeding / Dojenje
Compatible with pregnancy and breastfeeding / Kompatibilni s trudnoćom i dojenjem:				
Non-selective NSAIDs / Neselektivni NSAR	+	+ intermittent / intermitentno	+ intermittent / intermitentno – stop at 30 weeks / prekinuti od 30. tjedna	++
Prednisone / Prednizon	+ (<20 mg/d)	+ (<20 mg/d)	+ (<20 mg/d)	+ (after a dose >20 mg/d delay for 4 h / odgoditi 4 h kod doze >20 mg/d)
Hydroxychloroquine / Hidroksiklorokin ≤400 mg/d	++	++	++	++
Sulfasalazine / Sulfasalazin	++ (with folic acid / s folnom kiselinom)	++ (with folic acid / s folnom kiselinom)	++	+ (if healthy, full-term infant / kod donesenog, zdravog dojenčeta)
Azathioprine / Azatioprin	++	++	++	+
Colchicine / Kolhicin	++	++	++	++ (delay for 2–4 h / odgoditi 2–4 h)
Dapsone/ Dapson				
Ciclosporin / Ciklosporin	++	+ (monitor blood pressure, glucose, creatinine / pratiti arterijski tlak, glukozu, kreatinin)	+ (monitor blood pressure, glucose, creatinine / pratiti arterijski tlak, glukozu, kreatinin)	+
Tacrolimus / Takrolimus				
TNF INHIBITORS / TNF INHIBITORI				
Certolizumab / Certolizumab	++	++	++	++
Infliximab / Infliksimab	++	++	+ (until 20 weeks / do 20. tjedna)	++
Etanercept / Etanercept	++	++	+ (until 30–32 weeks / do 30–32. tjedna)	++
Adalimumab / Adalimumab	++	++	+ (until 28 weeks / do 28. tjedna)	++
Golimumab / Golimumab	++	++	+ (until 28 weeks /do 28. tjedna)	++
OTHER bDMARDs / OSTALI bDMARD				
Abatacept / Abatacept	++ stop at conception / obustaviti kod začeća	+ in severe disease if there is no alternative / samo u teškoj bolesti ako nema alternativa	+ in severe disease if there is no alternative / samo u teškoj bolesti ako nema alternativa	++
IL-6 inhibitors / Inhibitori IL-6				
Rituximab / Rituksimab				
Belimumab / Belimumab				
IL-1 inhibitors / Inhibitori IL-1				
IL-17 inhibitors / Inhibitori IL-17				
IL-12/23 inhibitors / Inhibitori IL-12/23				
Not compatible with pregnancy and breastfeeding / Nekompatibilni s trudnoćom i dojenjem:				
COX-2 inhibitors / COX-2 inhibitori	+	––	––	–– (+celecoxib / celekoksib)
Methotrexate ≤ 25mg/week / Metotreksat ≤ 25mg/tjedno	stop 1–3 months / obustaviti 1–3 mjeseca	––	––	––
Leflunomide / Leflunomid	stop 24 months or carry out a cholestyramine washout / obustaviti 24 mjeseca ili kolestiraminski *washout*	––	––	––
Cyclophosphamide / Ciklofosfamid	stop 3 months / obustaviti 3 mjeseca	––	––	––
Mycophenolate Mofetil / Mikofenolatmofetil	stop 6 weeks / obustaviti 6 tjedana	––	––	––
JAK inhibitors / JAK inhibitori	stop 2 weeks / obustaviti 2 tjedna	––	––	––

Legend / legenda: ++ compatible / kompatibilan; + conditionally compatible / uvjetno kompatibilan; –– incompatible / nekompatibilan

ommendations, belimumab is considered to be compatible with breastfeeding, and according to the ACR it is conditionally recommended, while at the time when the EULAR's guidelines were published, there was no sufficient evidence on this matter (1, 2).

IL-1 INHIBITORS

IL-1 inhibitors are used in the treatment of periodic fever syndrome, Still's disease in children and adults (systemic-onset juvenile idiopathic arthritis (sJIA), adult-onset Still's disease (AOSD)) and gouty arthritis.

Anakinra is a recombinant IL-1 receptor antagonist (IL-1Ra) of high molecular mass that does not cross the placenta, while canakinumab is a human monoclonal antibody which binds to IL-1 with active placental transport from the second trimester. There is no evidence of their teratogenic effect and the exposure to IL-1 inhibitors during pregnancy is probably not harmful, however the safety data on their use are limited. The ACR and the EULAR only give recommendations for anakinra, and the BSR gives a joint recommendation for both IL-1 inhibitors. It is recommended to discontinue IL-1 inhibitors at conception/pregnancy, but their administration during pregnancy may be considered for the control of severe maternal disease if no other compatible drug is available (1–3). With foetal exposure in the third trimester, it is recommended to postpone live vaccines until after the 6th month of the infant's life. According to the BSR recommendations, IL-1 inhibitors are considered to be compatible with breastfeeding. According to the ACR recommendations, anakinra is considered to be conditionally recommended for use during breastfeeding, and at the time when the EULAR's guidelines were published, there was no sufficient evidence on this matter (1, 2).

IL-17 INHIBITORS

IL-17 inhibitors are used rheumatology for the treatment of SpA, PsA and JIA.

The BSR has a joint recommendation for both IL-17 inhibitors, secukinumab and ixekizumab. For IL-17 inhibitors there is no evidence of their teratogenic effect, but there are limited safety data on their use. It is recommended to discontinue the use of IL-17 inhibitors in case of conception/pregnancy. In case of severe maternal illness, its administration during pregnancy can be considered if there is no other compatible drug. In case of foetal exposure in the third trimester, live vaccines should be postponed until after the 6th month of the infant's life (1).

When it comes to secukinumab, the ACR gives the same recommendation as the BSR, but it does not give a recommendation for ixekizumab(2). The 2016 EULAR guidelines do not state anything on IL-17 inhibitors because at that time, secukinumab (2015) and ixekizumab (2016) had just entered the market.

može se razmotriti davanje u trudnoći ako nema drugoga kompatibilnog lijeka. U slučaju izloženosti ploda u trećem tromjesečju živa cjepiva treba odgoditi do navršenih šest mjeseci života dojenčeta. Prema preporukama BSR-a ustekinumab se smatra kompatibilnim s dojenjem (1–3).

ANIFROLUMAB

Anifrolumab je humano IgG1 kapa monoklonsko protutijelo koje se vezuje za podjedinicu 1 receptora za interferon tipa I i koristi se u liječenju SLE. Još nema publiciranih dokaza niti preporuka za upotrebu anifrolumaba u trudnoći.

EKULIZUMAB

Ekulizumab je humanizirano anti-C5a monoklonsko protutijelo jedinstvene IgG2/4 kapa formulacije s oslabljenom Fc funkcijom, što mu teoretski limitira placentalni transfer. Ekulizumab nije uopće ili je tek u malim količinama detektiran u umbilikalnoj krvi, čak i kod upotrebe u kasnijoj trudnoći, što se objašnjava njegovom jedinstvenom strukturom. Ekulizumab se uz svoje indikacije (paroksizmalna hemolitička anemija, atipični hemolitičko-uremični sindrom i generalizirana miastenija gravis) pokazao učinkovitim u trudnica s refraktornim katastrofalnim antifosfolipidnim sindromom (C-APS) i HELLP sindromom (22). Ekulizumab je moguća terapijska opcija koju treba razmotriti za ova ozbiljna stanja uzrokovana aktivacijom komplementa u trudnoći. Zbog nedovoljnih dokaza o sigurnosti nijedne smjernice još ne komentiraju sigurnost ekulizumaba u trudnoći (15). Sumarni pregled kompatibilnosti reumatoloških lijekova s trudnoćom i dojenjem prikazan je u tablici 1.

REUMATOLOŠKI LIJEKOVI I OČINSTVO

Ekspozicija muškaraca prednizonu, hidroksiklorokinu, metotreksatu ≤ 25 mg/tjedno, leflunomidu, azatioprinu, ciklosporinu i takrolimusu, mikofenolatu, JAK-inhibitorima i biološkim lijekovima smatra se kompatibilnom sa začećem (1).

Ciklofosfamid je gonadotoksičan kako za žene tako i za muškarce te se prije ekspozicije ciklofosfamidu savjetuje razmotriti neku od metoda očuvanja fertiliteta kao što je krioprezervacija sjemena.

Sulfasalazin može uzrokovati reverzibilnu smanjenu plodnost muškaraca uzrokujući oligospermiju, smanjenu mobilnost spermija i povećan broj abnormalnih spermija (10).

ZAKLJUČAK

U današnje vrijeme upalne reumatske bolesti kod trudnica uglavnom je moguće učinkovito i sigurno li-

According to the BSR recommendations, IL-17 inhibitors are considered to be compatible with breastfeeding, and according to the ACR, secukinumab is conditionally recommended for use during breastfeeding (1, 2).

IL-12/23 INHIBITOR

The blockade of IL-12/23 is used in rheumatology for the treatment of PsA.

It is recommended to discontinue the use of ustekinumab in case of conception/pregnancy. There is no evidence of its teratogenic effect, but there are limited safety data on its use. In case of severe maternal illness, its administration during pregnancy can be considered if there is no other compatible drug. In case of foetal exposure in the third trimester, live vaccines should be postponed for after the 6th month of the infant's life. According to the BSR recommendations ustekinumab is considered to be compatible with breastfeeding (1–3).

ANIFROLUMAB

Anifrolumab is a human IgG1 kappa monoclonal antibody that binds to the to the type I interferon receptor subunit 1 and is used in the treatment of SLE. There is still no published evidence or recommendations for the use of anifrolumab in pregnancy.

ECULIZUMAB

Eculizumab is a humanized anti-C5a monoclonal antibody of a unique IgG2/4 kappa formulation with weakened Fc function, which theoretically limits its placental transfer. Eculizumab has little to no presence in umbilical cord blood, even when used in later pregnancy, which is explained by its unique structure. In addition to its indications, paroxysmal haemolytic anaemia, atypical haemolytic uremic syndrome and generalised myasthenia gravis, eculizumab has been shown to be effective in pregnant women with refractory catastrophic antiphospholipid syndrome (C-APS) and HELLP syndrome (22). Eculizumab is a possible therapeutic option to consider for these serious conditions caused by complement activation in pregnancy. Due to insufficient safety evidence, no guidelines yet provide information on the safety of eculizumab in pregnancy (15). A summary of the compatibility of rheumatological drugs with pregnancy and breastfeeding is shown in Table 1.

PATERNAL EXPOSURE TO ANTIRHEUMATIC DRUGS

Paternal exposure to prednisone, hydroxychloroquine, methotrexate ≤ 25 mg/week, leflunomide, azathioprine, cyclosporine and tacrolimus, mycophenoječiti. U ovom radu iznesen je sažetak recentnih smjernica najrelevantnijih stručnih organizacija u vezi planiranja trudnoće te primjene specifične farmakološke terapije koja se primjenjuje u imunološki posredovanim upalnim reumatskim bolestima.

Preporučuje se savjetovanje prije začeća i planiranje trudnoće nakon postizanja remisije bolesti. Savjetuje se pravodobna zamjena nekompatibilnih lijekova kompatibilnima i to u minimalnoj učinkovitoj dozi. U situacijama kada nema prikladnog i s trudnoćom kompatibilnog lijeka kontrola teške i po život opasne bolesti majke treba imati prioritet pred zabrinutošću za moguće štetne učinke za plod. Svi biološki lijekovi mogu se nastaviti kroz čitavu trudnoću ako su potrebni za kontrolu aktivnosti teške bolesti majke. Kod izloženosti biološkom lijeku *in utero* potrebno je prilagoditi kalendar cijepljenja, odnosno odgoditi živa cjepiva za najmanje šest mjeseci od ekspozicije, a potrebna su i dulja razdoblja praćenja novorođenčadi zbog mogućih kasnih učinaka poput rizika od maligniteta i odgođenih imunoloških učinaka.

Zahvala: Autori nisu naveli zahvale za ovaj rad.

Financiranje: Autori za ovaj rad nisu primili nikakva sredstva.

Izjava o sukobu interesa: Autori izjavljuju da nisu u sukobu interesa.

late, JAK inhibitors and biologics is considered to be compatible at conception (1).

Cyclophosphamide has a gonadotoxic effect for both women and men, and before exposure to cyclophosphamide it is advised to consider one of the fertility preservation procedures such as sperm cryopreservation.

Sulfasalazine may cause reversible male infertility by causing oligospermia, reduced sperm motility and increased abnormal sperm counts (10).

CONCLUSION

Nowadays, it is mostly possible to effectively and safely treat inflammatory rheumatic diseases in pregnant women. This paper presents a summary of recent recommendations of the most relevant professional associations regarding pregnancy planning, and the application of specific pharmacological therapy used in immune-mediated inflammatory rheumatic diseases.

It is recommended to consult with your physician before conception and pregnancy planning and after achieving remission. It is recommended to replace non-compatible drugs with compatible ones in a timely manner and to use them in the minimum effective dose. In cases where there is no suitable drug that is compatible with pregnancy, the control of the mother's severe and life-threatening disease should take priority over concerns for potentially adverse foetal outcomes. The use of all biologic drugs can be continued throughout the pregnancy if they are necessary to establish control over the activity of the mother's severe disease. In case of exposure to a biologic drug in utero, it is necessary to adjust the immunisation schedule, i.e. postpone live vaccines for at least six months after exposure- In addition to that, longer periods of follow-up of newborns are required due to possible late effects such as the risk of malignancy and delayed immune-related events.

Acknowledgments: The authors report no acknowledgments.

Funding: For this work authors did not receive any funding.

Conflict of interest statement: The authors declare no conflict of interest.

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