

Conventional synthetic disease-modifying antirheumatic drugs (csDMARD) in rheumatoid arthritis during pregnancy and lactation: a review

Andy Kurniawan Saputra*, Desy Purnamasari, Laras Ratna Sari, Nunuk Wijayanti, Yulianasari Pulungan

Master Program of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta
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ABSTRACT

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Rheumatoid arthritis (RA) is an autoimmune and prominent inflammatory disorder that can affect wide of variety body systems, mainly joints. In Indonesia, the prevalence of RA is about 7.3% and mostly are women. The majority of women with RA are at childbearing and can be worsening throughout pregnancy and lactation. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are the most common used medicine in RA for pregnancy and lactation. This scoping review was conducted using publications obtained from PubMed, Embase, The Cochrane Library, POPLINE, and Google Scholar concerning the safety of csDMARD in rheumatoid arthritis during pregnancy and lactation from 2011 to 2021. Among csDMARDs reviewed, sulfasalazine, hydroxychloroquine, chloroquine, and cyclosporine are relatively safe for pregnant and lactating women. However, they should be used in caution by considering the risk and benefit as well as under clinical supervision.

ABSTRAK

Artritis reumatoid (AR) adalah penyakit autoimun dan inflamasi yang menyerang berbagai sistem tubuh terutama persendian. Prevalensi AR di Indonesia sekitar 7,3% dan sebagian besar diderita wanita. Sebagian besar perempuan dengan AR berada dalam masa subur dan dapat meningkat keparahannya selama kehamilan dan laktasi. Obat antirematik pemodifikasi penyakit sintetis konvensional (*conventional synthetic disease-modifying antirheumatic drugs/ csDMARDs*) adalah obat yang umum digunakan untuk AR pada kehamilan dan laktasi. Telaah pustaka ini dilakukan menggunakan publikasi tahun 2011 sampai 2021 dari PubMed, Embase, The Cochrane Library, POPLINE, and Google Scholar tentang csDMARD pada AR selama kehamilan dan laktasi. Di antara csDMARD yang ditelaah, sulfasalazine, hidrosiklorokuin, klorokuin dan siklosporin relatif aman untuk wanita hamil dan menyusui. Namun, penggunaannya harus mempertimbangkan manfaat dan risikonya serta di bawah pengawasan dokter spesialis.

*corresponding author: kurniawandy@hotmail.com

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune and prominent inflammatory disorder that can affect wide of variety body systems, mainly joints. The etiology of RA is well unknown however genetic and environmental factors such as smoking and obesity seem to play a role in the disease.¹ In Indonesia, the prevalence of RA is 7.3% and mostly are women.² The majority of women in RA are of childbearing age and disease severity improves throughout pregnancy and lactation.

The therapy of RA includes non steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and disease-modifying antirheumatic drugs (DMARDs). The DMARDs are categorized into two groups, those are biological DMARDs (bDMARDs) and synthetic DMARDs (conventional synthetic DMARDs/csDMARDs) and targeted synthetic DMARDs (tsDMARDs).³ Food and drug administration (FDA) has established five level medication risk categories in pregnancy i.e. A, B, C, D and X, also the effect of the medication if it is used during lactation. From the therapy groups, csDMARDs are often used in pregnancy and lactation. Even though, it was reported that the csDMARDs are highly teratogenic, harmful to the mother and could affect the fetus in the lactation period.³ We reviewed here the safety of some csDMARDs included sulfasalazine, leflunomide, azathioprine, hydroxychloroquine, chloroquine, tacrolimus, cyclosporine and methotrexate to treat RA during pregnancy and lactation. Hopefully, it could assist clinicians to choose the appropriate csDMARD to treat the disease.

METHOD

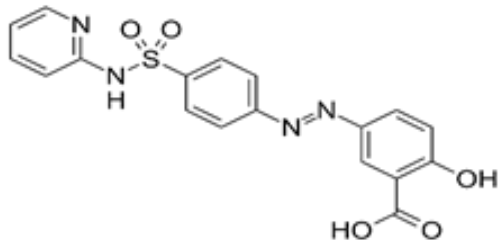
This scoping review was undertaken

by PubMed, Embase, The Cochrane Library, POPLINE and Google Scholar for studies addressing the safety of csDMARD in rheumatoid arthritis during pregnancy and lactation from 2011 to 2021. The following search terms were used in combination: “rheumatoid arthritis”, “pregnancy”, “lactation”, “csDMARD”. We included any articles written in English, including review, pre-clinical and clinical studies. We excluded any article which was published under 2011.

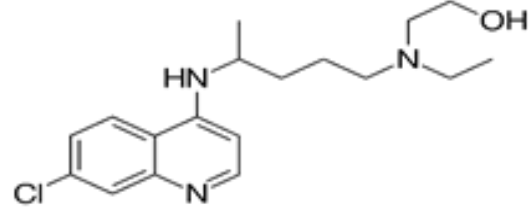
RESULT AND DISCUSSION

We conducted data collection from 2011 to 2021. PubMed showed 42 studies, 1 study from Embase and 1 study from Google Scholar, in total we conducted 44 studies of csDMARD treatment in RA in pregnancy and lactation. All studies are included in this review.

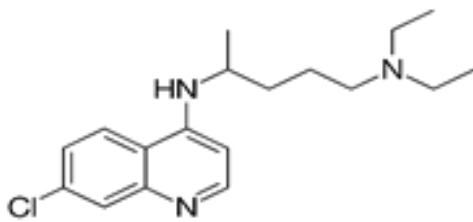
Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are the first-line treatment for RA recommended by FDA. The csDMARDs work by suppressing the immune system and inflammatory responses by inhibiting T cells and B cells that are responsible for the progression of RA. Its efficacy and safety have been established in many randomized controlled trials (RCTs) and are now widely used to treat the disease.⁴ The csDMARDs are composed of sulfasalazine, leflunomide, azathioprine, hydroxychloroquine, chloroquine, tacrolimus, cyclosporine and methotrexate (FIGURE 1). In this review, we informed the new update of RA treatment for pregnancy and lactation from 2011 to 2021. These drugs have different FDA category drugs in pregnancy and have a different effect in lactation and fertility. The pharmacological profile of each of csDMARDs will be reviewed below.



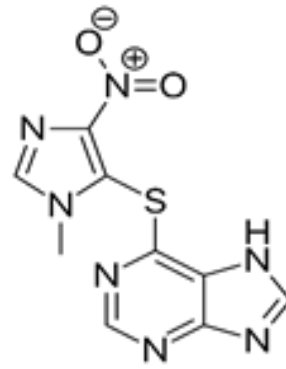
Sulfasalazin



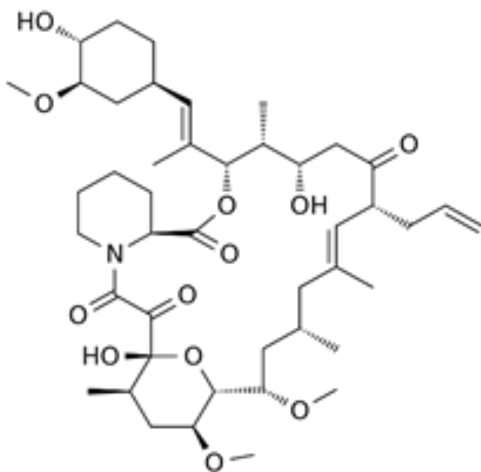
Hydroxychloroquine



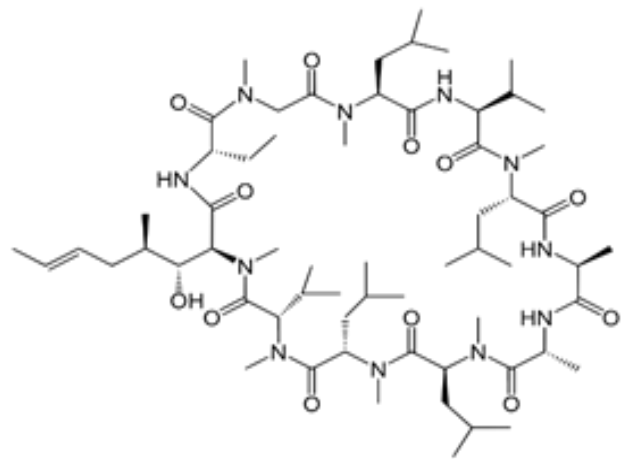
Chloroquine



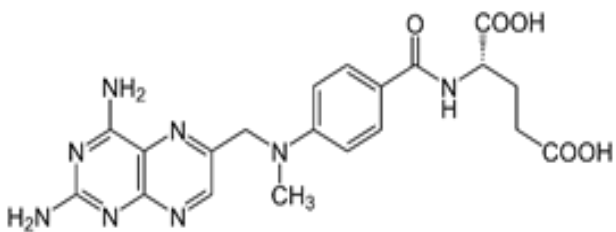
Azathioprine



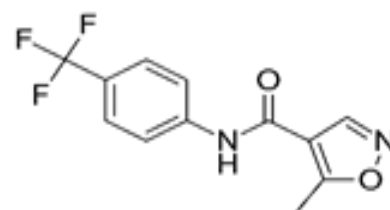
Tacrolimus



Cyclosporine



Methotrexate



Leflunomide

FIGURE 1. Chemical structure of csDMARDs

TABLE 1. Summary of the safety profile of csDMARDs in pregnancy and lactation

csDMARDs	FDA category	Preclinical/ clinical study	Pregnancy	Lactation
Sulfasalazin	B	Clinical study (Observational)	1 - 2 g/daily: no fetal effects > 2 g/daily: congenital neutropenia <i>Recommend to use folic acid 5 mg/day to prevent another side effect.</i>	Safe, but should be avoided to premature, hyperbilirubinemia and jaundice infants
Hydroxychloroquine	C	Clinical study (Observational)	Hydroxychloroquine crosses the placenta as fetus levels were shown to be equivalent to maternal levels	There were no adverse effects on growth, development, motor skills and retinal findings in patients with hydroxychloroquine administration during lactation
Chloroquine	Not classified yet	Clinical study (Observational)	There was no increased risk of major birth defects, preterm birth or small size for gestational age	Relatively safe, and compatible with lactation
Cyclosporine	C	Clinical study (Observational)	Dosage of 2 - 3.5 mg/kg/day does not increase the risk of premature or low birth weight	The estimated infant exposure to cyclosporine via breast milk was minimal
Tacrolimus	C	Clinical study (Observational)	Several cases showed fetus complications including low birthweights and spontaneous abortion	The study of tacrolimus safety for lactation is still limited
Azathioprine	D	Clinical study (Observational)	Dosage 100 mg per day. There were no significant differences in the rate of miscarriages, ectopic pregnancies or still births between azathioprine and control groups, but the crude rates of voluntary abortion and intrauterine death were slightly, but not significantly higher in the azathioprine than in the control group	Azathioprine is compatible with breastfeeding
Methotrexate	X	Clinical study (Observational)	Methotrexate is teratogenic, inflicting a characteristic collection of abnormalities in neonates exposed in utero	Breastfeeding during methotrexate treatment is not recommended because the drug is excreted into breast milk in low concentrations and may accumulate in neonatal tissues
Methotrexate	X	Preclinical study (Experimental) and clinical study (Observational)	Experimental animal studies in rats, rabbits, and mice have demonstrated that leflunomide is embryotoxic and teratogenic. In human, dosage 2,5 - 100 mg/day of leflunomide give higher rate of preterm delivery before 35 weeks pregnancy and more likely to deliver by cesarean section	Leflunomide has a long half-life (14 days) and there are insufficient data on leflunomide levels in breast milk or infant serum, so it is considered incompatible with lactation.

Sulfasalazine

Sulfasalazine is one of csDMARD that is frequently used to treat RA in pregnancy and lactation since it has been classified in FDA category B drug. It can be used as monotherapy or in combination with other DMARDs as an effective treatment for mild to moderate RA. In fertility and conception, sulfasalazine is not associated with impaired fertility in women. For men, it could increase the risk of oligospermia, abnormal spermatozoa, reduced sperm motility and temporary infertility because of its metabolite sulfapyridine. This effect can be reduced with the discontinued sulfasalazine. Sulfasalazine is advisable in pregnancy with dose ranging from 1-2 g/day orally. It did not show increased congenital malformations, morbidity and mortality rates but a dose of more than 2 g/day could accelerate rates of reversible congenital neutropenia. Moreover, sulfasalazine has a potent inhibitor of reduced folate carrier effect, since folate is an important aspect to prevent a major birth defect of the fetus's brain and spine. It is recommended to add folate supplementation 5 mg/day to prevent this side effect. In lactation, around 5.9% of sulfasalazine is secreted in breast milk. However, no any harmful effects in infants exposed to sulfasalazine were reported. Women who have premature, hyperbilirubinemia and jaundice infants should be avoided to use sulfasalazine.^{3,5,6}

Hydroxychloroquine

Hydroxychloroquine as an antiautoimmune therapy exerts its effects by inhibiting TLR-mediated cell activation and cytokine production. Hydroxychloroquine also inhibits antigen processing and subsequent MHC class II presentation to T cells, preventing T cell activation, differentiation and expression of co-stimulatory molecules (such as CD154) and also reducing the production of

cytokines (such as IL-1, IL-6 and TNF) by both T cells and B cells.⁷ There was no evidence in elevated prevalence of major malformation congenital in fetus who have been overt since the first trimester of pregnancy, but it is the third study to suggest a moderate increased risk. For most patients with autoimmune rheumatic disorders, the benefits of treatment during pregnancy will likely outweigh the risk.^{8,9} There are no reports of adverse effects of hydroxychloroquine on male fertility.¹⁰ The continuation of this drug during pregnancy at higher dose has been controversial and FDA classified this drug in category C.¹¹ Hydroxychloroquine crosses the placenta as fetus levels were shown to be equivalent to maternal levels. There was no fetal toxicity in subsequent studies and no congenital abnormalities were observed in pregnancy treated with hydroxychloroquine during the first trimester of pregnancy.¹² Physicians must be aware of the possibility of significant concentrations of hydroxychloroquine exposing the fetus during pregnancy. There were no adverse effects on growth, development, motor skills and retinal findings in patients with hydroxychloroquine administration during lactation. The duration of exposure of the infants through breast milk ranged between 1 to 86 months and the maternal dose varied between 200 to 400 mg/day.¹³ The daily therapeutic dosage of hydroxychloroquine in adults is 6.5 mg/kg body weight, and the hydroxychloroquine ingestion by infants corresponded to 0.06 and 0.2 mg/kg per day.¹⁴

Chloroquine

Chloroquine as an antiautoimmune therapy shows its effect by preventing differentiation and binding to transcriptional factors on T helper 17 cells. Chloroquine, also driving the formation of regulatory T cells, activates the transcription factors Foxp3. Regulatory T cells have been

shown to treat and prevent autoimmune diseases.¹⁵ *In vitro* studies suggest that chloroquine may negatively impair sperm motility, but no clinical data are available.^{16,17} The FDA has not categorized chloroquine in pregnancy. There are no controlled studies in human pregnancies.¹⁸ In a cohort study, among 1487 pregnancies exposed to 4-aminoquinolines (1184 chloroquine and 303 hydroxychloroquine-exposed), there was no increased risk of major birth defects, preterm birth or small size for gestational age.¹² It was consistent with the recent study conducted by Bérard *et al.*¹⁹ It found that among 288 pregnancies exposed to chloroquine (183 pregnancies) and hydroxychloroquine (105 pregnancies) which used for 71.8 days on average, at a dose of 204.3 mg/day, did not showed any increased risk related to chloroquine/hydroxychloroquine exposure for prematurity, low birth weight or major congenital malformations. Despite theoretical concerns of retinal toxicity and ototoxicity extrapolated in pregnancy, chloroquine is relatively safe, and compatible with pregnancy and lactation.^{18,20}

Cyclosporine

Similar to tacrolimus, cyclosporine exerts its effect by inhibiting calcineurin, binds cyclophilin, blocks T cell activation and inhibits cytokine transcription.²¹ Cyclosporine improved sperm motility in men with antisperm antibodies. It also showed normal semen parameters and testicular function.²² Cyclosporin is classified in category C as pregnancy risk by the FDA. Around 6% of the maternal concentration of cyclosporine was accounted for in fetus blood and the drug was not detectable in either the maternal or fetus brain. Cyclosporine can be used during pregnancy and found that dosage of 2 - 3.5 mg/kg/day does not increase the risk of premature or low birth weight.²³ Analysis revealed that the estimated

infant exposure to cyclosporine via breast milk was minimal and provided reassurance to continue breastfeeding in this case.²⁴

Tacrolimus

Tacrolimus as an antiautoimmune therapy exerts its effects by inhibiting calcineurin, binds FK506 binding protein, blocks T cell activation and inhibits cytokine transcription.²⁵ Tacrolimus is classified in category C as teratogenic risk by the FDA.²⁶ The study on tacrolimus safety in pregnancy and newborn is still limited. Aktürk *et al.*²⁷ reported that there were several cases which showed fetus complications including low birthweights and spontaneous abortion. Another study from Nakagawa *et al.*²⁸ reported that tacrolimus administration before and during pregnancy is not associated with obstetrical and perinatal complications. The British Society for Rheumatology (BSR) and British Health Professional in Rheumatology (BHPR) suggested that tacrolimus is compatible throughout pregnancy at the lowest effective dose.²⁹

Azathioprine

Azathioprine is one of the immunosuppressive antimetabolite agents. In general, azathioprine is an antimetabolite and is administered according to guidelines for cytotoxic drugs. Azathioprine is a purine analog that is metabolized to thioguanine and mercaptopurine. Thioguanine is inactivated by hypoxanthine-guanine phosphoribosyltransferase (HPRT).³⁰ Thioguanine nucleotides are responsible for inhibiting DNA synthesis, thus causing cytotoxicity to cells.³¹ Mercaptopurine is inactivated by thiopurine methyltransferase (TPMT). It inhibits the nucleic acid synthesis and affects cellular and humoral immune functions.^{32,33} Patients should have TPMT testing before receiving azathioprine.³⁴ If the activity of that enzyme is low,

patients may experience more severe toxicity. Myelosuppression and GI adverse effects correlate with TPMT polymorphism, but hepatotoxicity may not present. Other metabolic pathways are also involved in the elimination of azathioprine.³² The metabolism of azathioprine and mercaptopurine is inhibited by allopurinol and febuxostat. If the combination of these drugs is to be used, a reduction in dose is required.³⁵ Initial dose azathioprine oral 1-2.5 mg/kg daily administered once or twice daily.^{3,36} Low-dose corticosteroids and NSAIDs may be continued in patients with RA during pregnancy and lactacy.³ Damage to the trophoblast resulting in the destruction of embryonic tissue has been demonstrated in pregnant rats exposed to azathioprine at doses of 20 mg/kg daily but was not seen in doses of 2 or 4 mg/kg/day.³⁷ Most information regarding azathioprine safety during human pregnancy has been derived from its use in the transplant and inflammatory bowel disease populations. In a study administration of azathioprine to pregnant mothers and subsequent measurement of azathioprine and its metabolites in amniotic fluid and fetal blood, only thiouric acid, the inactive metabolite, was detectable in significant quantities. The low concentration of active metabolites of azathioprine has been related to the lack of inosinate pyrophosphorylase in the fetus, which is required for conversion of azathioprine to thioinosinic acid, the determinant of azathioprine toxicity in dividing cells. The frequency of congenital anomalies in the offspring of women receiving azathioprine for renal transplant ranged from 0% to 11.8% with no pattern identified.³⁷ The recommendation of the Indonesian Rheumatology Association to the preparation of this drug is to perform complete peripheral blood tests, creatinine, liver function, and albumin levels. Monitoring for drugs is peripheral blood tests (every 4-12 weeks), creatinine (every 6 months) and liver function (yearly).³

Azathioprine is classified in category D as pregnancy risk by the FDA. However, based on the current evidence of its safety in pregnancy, azathioprine may be used during pregnancy. There were no significant differences in the rate of miscarriages, ectopic pregnancies or still births between azathioprine and control groups, but the crude rates of voluntary abortion and intrauterine death were slightly, but not significantly higher in the azathioprine than in the control group.³⁸ In lactation, azathioprine level is not useful in assessing breast milk levels. However, several case series suggest that this medication may present a low risk to the nursing infant. The recommendation from the Indonesian Rheumatology Association does not to use azathioprine during breastfeeding even if the level in breast milk is not significant.³

Methotrexate

Methotrexate is a folic acid antagonist used in treatment of cancer, psoriasis, and many rheumatic diseases. It is commonly used DMARD for RA and is usually administered orally at a dose of 5 to 20 mg/weekly.³⁹ The mechanism of action of methotrexate is increase adenosine levels and on engagement of adenosine with its extracellular receptors an intracellular cascade is activated promoting an overall anti-inflammatory state.⁴⁰ During treatment with methotrexate, patients should receive additional folic acid. Methotrexate is one of csDMARD that is frequently used to treat RA in pregnancy and lactation since it has been classified in FDA category X drug.³ In fertility and conception, methotrexate does not seem to adversely affect female fertility. Moreover, methotrexate therapy can cause reversible sterility in men. Women who wish to become pregnant should discontinue treatment with the drug for at least 3 months prior to attempting conception.⁴¹ In pregnancy, methotrexate is teratogenic, inflicting a

characteristic collection of abnormalities in neonates exposed in utero. The pattern of congenital abnormalities is known as the aminopterin/methotrexate syndrome and includes growth deficiency, hypoplastic supraorbital ridges, abnormal cranial ossification, small low-set ears, micrognathia and limb abnormalities. Methotrexate shows the most damage at 5- to 8-weeks gestation.³⁹ In lactation, methotrexate treatment is not recommended because the drug is excreted into breast milk in low concentrations and may accumulate in neonatal tissues. The American Academy of Pediatrics considers methotrexate to be contraindicated during lactation because of several potential problems, including neutropenia, immune suppression, adverse effects on growth, and carcinogenesis.⁶

Leflunomide

Leflunomide is a de novo pyrimidine synthesis inhibitor and used to prevent long-term joint damage and improve joint symptoms in patients with RA. It also inhibits T-cell proliferation and protein tyrosine kinases, which is necessary for intracellular signal transduction. The FDA classified leflunomide as category X and contraindicated in pregnancy because on animal reproduction studies reported both embryotoxic and teratogenic effects, mainly leading to growth retardation and craniofacial and skeletal malformations.⁴² Experimental animal studies in rats, rabbits, and mice have demonstrated that leflunomide is embryotoxic and teratogenic. Malformations of the head (including cranioschisis and exencephaly), ribs, vertebral column, rump and limbs were observed in rats. Head and skeletal defects were noted in rabbits. Multiple malformations, including craniofacial defects and anomalies of the axial skeleton, great vessels and heart, were observed in mice.⁴³

Women of reproductive age who are likely to become pregnant are advised

to consider using contraception to avoid pregnancy. Women who are taking leflunomide and planning to become pregnant should undergo an elimination procedure to eliminate leflunomide metabolites in plasma to below 0.02-1/L. The wash out procedure was carried out by consuming cholestyramine 8 g orally, 3 times a day for 11 days or until the leflunomide metabolite level in plasma reached the desired level. Without a wash out process, the procedure can take up to 2 years to reach that level.⁴³ Leflunomide has a very long half-life of 14 days. There is not enough data showing the safety of leflunomide in lactation like leflunomide level in the breast milk or infant serum level and also the long half-life, the use of leflunomide in lactation should be avoided.^{6,17}

CONCLUSION

In conclusion, sulfasalazine, hydroxychloroquine, chloroquine and cyclosporin are relatively safe for pregnant and lactating women. However, they should be used under clinical supervision and the treatment of RA in pregnancy and lactation should be used in caution and considered the risk and benefit. Further study in the long term therapy on a larger population is needed.

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