Review
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Rheumatic Diseases and Their Treatment with Anti-Rheumatic Drugs during Pregnancy

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Abstract

Many rheumatic diseases affect women of childbearing age. It is well known that during pregnancy, some patients with inflammatory arthritis such as rheumatoid arthritis go into remission, whereas in others, pregnancy aggravates disease activity. Unfortunately, the flares of rheumatic diseases during pregnancy may result in fetal loss, intrauterine growth retardation, and premature delivery. Furthermore, during pregnancy, anti-rheumatic drugs used to control disease activity may lead to fetal complications. In this review, the effects of pregnancy on the disease and the effects of disease on the fetus are discussed first. The effects of biological and non-biological disease-modifying anti-rheumatic drugs on fertility, pregnancy, and lactation are then summarized. Physicians dealing with rheumatic diseases need to be aware of the potential adverse effects of these medications and discuss the risks and benefits of drugs during pregnancy and lactation with their patients in detail.
Keywords: Rheumatic diseases, medication, pregnancy, lactation

Introduction

Majority of rheumatic diseases are seen in women of childbearing age. Specialists involved in the diagnosis and treatment of these diseases often confront patients who want to become pregnant or who have unplanned pregnancies. In the past, avoiding pregnancy was often recommended because possible complications in mothers and babies could be avoided, and complex effects of sex hormones on the immune system remained unclear. Today, however, thanks to the fact that the course of these diseases during pregnancy is more clearly known and because of new developments in treatment, it has become possible for patients to have healthy babies at the end of a pregnancy under a close follow-up (1).

Because of physiological changes during pregnancy, differences occur in the absorption, distribution, metabolism, and excretion of drugs. Consequently, the effects of drugs may vary. Detailed information about the effects of drugs on fertility and possible fetal and maternal complications should be provided to male patients and female patients with a potential to become pregnant. A treatment plan clarifying the benefits and risks of drugs to be used during pregnancy and lactation should be established in consultation with patients. Otherwise, the uncontrolled discontinuation of all drugs used before pregnancy by patients can adversely affect fetal development and cause disease exacerbation. Similarly, accidental exposure of the fetus to harmful drugs may lead to very severe adverse effects.

The purpose of this compilation is to present information about the course of some common rheumatic diseases during pregnancy and to discuss maternal and fetal effects for individ-

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ual diseases. Additionally, we attempted to summarize information about the use of medicines in the treatment of rheumatic diseases during pregnancy and lactation.

Pregnancy and Rheumatic Diseases

Rheumatoid Arthritis

The disease activity of rheumatoid arthritis (RA) decreases during pregnancy, and remission is observed in 75%–95% patients. Recovery starts in the first trimester and continues during pregnancy (2, 3). RA remission at the initial stages of pregnancy indicates that it will be in remission during later pregnancies. Conversely, if remission does not occur during the first pregnancy, it cannot be expected during subsequent pregnancies. After pregnancy, the RA exacerbation rate is relatively high in the first 3 months, but it causes moderate clinical signs only in 40% of patients (4). Prolactin has proinflammatory effects and may be responsible for exacerbation (1). Similarly, the risk of exacerbation increases after abortion. Although the possibility of occurrence of RA for the first time during pregnancy is very low, it is four times more likely to emerge in the postpartum period. It has even suggested that oral contraceptives decrease the RA development risk and have protective effects (5).

Although it is considered that RA does not cause infertility, the period of becoming pregnant in majority of patients is over 12 months and patients cannot be optimally treated during this period. From this point onward, in a fairly new study (6), the period until pregnancy was reported to be longer in those who were at an advanced age or were nulliparous, those with a high disease activity, or those who used non-steroidal anti-inflammatory drugs (NSAIDs) or prednisone >7.5 mg/day. A significant relationship was not found between this time and smoking, disease duration, rheumatoid factor positivity, and sulfasalazine and methotrexate use.

The reported results about fetal complications such as abortion, stillbirth, low birth weight, and prematurity that may occur in patients with RA are contradictory. Vaginal delivery may be difficult in those with severe hip arthritis or prosthesis. When cesarean delivery is necessary under general anesthesia, any adverse effect is not in question in patients with cervical spine involvement, except for the risk of atlantoaxial subluxation.

Juvenile Chronic Arthritis

The remission rate of juvenile chronic arthritis (JCA) during pregnancy is unfortunately not as high as that for adult RA during pregnancy. Among the subtypes of JKA, a polyarticular form resembling adult RA has the highest remission rate, and patients with the condition show a recovery rate of approximately 60%. Postpartum exacerbation occurs in this disease as well. In a population-based study (7), it was determined that those with JKA have preeclampsia, premature birth, postpartum hemorrhage, and a higher rate of severe maternal morbidity.

Spondyloarthropathies

Very little data related to pregnancy are available in this group of diseases; despite this, although recovery is observed in peripheral arthritis and uveitis in majority of patients, there is deterioration in approximately 25% of them, mainly in those with axial involvement. This deterioration may be the result of postural changes that occur during pregnancy and the laxity of ligaments because of relaxin. In these patients, the exacerbation risk for both axial and peripheral joint symptoms increases during the first 6 months after birth (1, 8).

Although the disease activity of ankylosing spondylitis has been reported to not change during pregnancy, a recovery in enteropathic or psoriatic spondyloarthropathies as well as disease activity changes in patients with ankylosing spondylitis were reported by prospective studies conducted later. In a study in which nine pregnant women with ankylosing spondylitis were followed up (9), it was reported that disease activity increased in the second trimester and decreased in the third trimester. In another study (10), it was determined that significant improvements in pain occurred, particularly in the first trimester, but that pain increased in the following periods; the study also suggested that this was the result of an increased biomechanical load. In addition, women with ankylosing spondylitis have rates of fertility and normal birth similar to those in healthy communities (11).

Systemic Lupus Erythematosus

Although there are contradictory results in terms of whether pregnancy increases the risk of exacerbations in patients with systemic lupus erythematosus (SLE, it is generally accepted that pregnancy increases the disease activity. Exacerbation may occur during any period of pregnancy or after childbirth (1). Typically, an increase is observed in cutaneous, arthritic, and hematologic symptoms. If there is a history of exacerbation within the last 6 months before pregnancy or active lupus nephritis, if the disease remained very active in the past or if drug use was interrupted, the risk of exacerbation increases (12, 13). Patients with SLE have been reported to be as fertile as women in the general population. However, a decrease may occur in the fertility of patients because of amenorrhea resulting from renal failure in those with renal involvement, ovarian failure developing as a result of cyclophosphamide therapy, or menstrual irregularities that may occur in patients with high-dose corticosteroid therapy and anovulatory cycles (8). In addition, antiphospholipid syndrome occurring in patients with SLE can also cause infertility by venous thrombosis in the ovaries. These patients should use low-dose aspirin or heparin. It is recommended that after the drug is discontinued, at least three menstrual periods should pass in patients using cyclophosphamide and that the warfarin should be switched to heparin.

The major risk factor for disease exacerbation during pregnancy is the level of disease activity before pregnancy (14). Therefore, if a patient with SLE wants to become pregnant, it should happen in the period of remission. The risk of fetal and maternal complications is high in patients with active lupus nephritis. Therefore, lupus nephritis should be in remission for the last 6 months before pregnancy. Remission stable renal functions were defined as follows: serum creatinine and C3 are at normal levels, the number of urine erythrocytes is below 5, and the amount of urinary protein is below 0.5 g/day (1). Pregnancy is safer in patients whose serum creatinine level is ≤1.5 mg/dL,

urinary protein excretion is ≤3 g/day, and creatinine clearance is >60 ml/min (15). Severe pulmonary hypertension, heart failure, severe restrictive lung disease, moderate/severe chronic renal failure, high-dose (>25–30 mg/day) steroid treatment, disease exacerbation within the last 6 months despite aspirin and heparin therapy in previous pregnancies, severe pre-eclampsia, or HELLP syndrome development are among situations where pregnancy should be avoided (16).

In patients with an active disease, an increase is in question in preeclampsia risk depending on the use of corticosteroids, hypertension, gestational diabetes, infection, and early rupture of membranes (17). Accurately making the distinctive diagnosis of lupus nephritis and preeclampsia is very important to ensure effective treatment. Abortion, premature birth, intrauterine growth restriction, stillbirth, and hydrops fetalis are also among fetal complications (1). In addition, it must be kept in mind that can occur in the children of patients with SLE. Neonatal lupus is a syndrome that develops depending on the passage of the anti-Ro and anti-La antibodies from the mother to the fetus, and its most important complication is congenital heart block. Other symptoms are skin rash (most common), cytopenia, and hepatosplenomegaly, and these symptoms are usually temporal. These autoantibodies exist in approximately one-third of patients, and they pass through the placenta between 16th and 32nd weeks of gestation only in 5% of them (18, 19).

Due to exacerbation and complications that may arise during pregnancy, patients with SLE are required to be followed up monthly in terms of rheumatic diseases. It is useful to examine the basal antinuclear antibody, anti-dsDNA, complements, anti-Ro, anti-La, complete blood count, complete urinalysis, creatinine clearance, and urinary protein level in 24-h urine in the first visit. The disease activity index should be evaluated at each control, and patients should be closely monitored in terms of hypertension and renal function (20). Hypertension is found in approximately 25% of patients, and it is more common in those receiving corticosteroid treatment and those with a history of lupus nephritis (1).

Vasculitides

Because vasculitides, unlike RA and SLE, are more frequently encountered in males and at young ages, they rarely lead to pregnancy complications. Apart from idiopathic vasculitis and SLE vasculitis, the most common type of vasculitis during pregnancy is Takayasu disease, which causes hypertension, congestive heart failure, and renal failure. Subsequent complications of pregnancy in these patients have been reported as pre-eclampsia, antepartum hemorrhage, and stroke (1, 17, 21). Wegener's granulomatosis may be seen before, during, or after pregnancy in women of childbearing age. The period when exacerbation occurs most frequently is the first or second trimester of pregnancy or the first month of postpartum. Polyarteritis nodosa and Churg–Strauss vasculitis may also exacerbate during pregnancy or in the postpartum period. Because active or uncontrolled vasculitis increases the risk for fetal and maternal complications, it is necessary to inactivate the disease before pregnancy (21, 22). Moreover, the history of premature delivery in patients with vasculitis is also common (1).

Behçet's Disease

The course of the disease during pregnancy is variable, and there may be an exacerbation or recovery. The exacerbation rate was found to be lower in patients using colchicine than in those who did not. Exacerbation is observed particularly in oral/genital ulceration and ocular findings. Lesions of the central nervous system rarely occur. An increased risk of thrombosis exists with the impact of the disease as well as pregnancy (23). There are no adverse effects on the fetus and newborn. Although intrauterine growth retardation, abortion, and preterm birth have rarely been identified, the incidence of these cases was similar to that in the general population. Obstetric complications have also been reported to be closely associated with venous thrombosis (23, 24).

Systemic Sclerosis

Although approximately 60% of patients remain in stable disease during pregnancy, half the remaining patients show exacerbation and the other half show recovery. Because systemic sclerosis starts at 40–50 years of age, it is believed to have no effect on fertility (1). However, the following factors can cause a decrease in fertility: vaginal dryness, dyspareunia, and menstrual irregularities or cyclophosphamide use to treat associated organ involvement.

The most serious complication in patients with systemic sclerosis is renal crisis. Renal crisis mostly occurs in patients whose symptom duration is <5 years, in whom antitopoisomerase and anti-RNA polymerase III antibodies are positive, or in those who use a high dose of corticosteroids (25). Another important complication is pulmonary hypertension; the risk of mortality is approximately 50%. Moreover, it is recommended to postpone pregnancy in patients with restrictive lung involvement and malabsorption. Preeclampsia, premature rupture of membranes, excessive vaginal bleeding, abortion, prematurity, low birth weight, and neonatal death can be considered as other possible complications because of scleroderma during pregnancy (26).

Sjögren's Disease

There is no evidence that it impairs fertility. However, a relationship was determined between Sjögren's disease and endometriosis; therefore, it may indirectly cause infertility (27). In patients with Sjögren's disease, the rates of pregnancy complications such as spontaneous abortion, prematurity, and low birth weight are higher than in controls (28). Congenital heart block, idiopathic cardiomyopathy, and neonatal lupus syndrome may also develop (29) in the babies of patients with positive anti-Ro antibodies.

Dermatomyositis/Polymyositis

The risk of exacerbation of the disease during pregnancy is approximately 40%. If exacerbation occurs in the first trimester, the fetal mortality rate can increase to up to 62% (30). Pregnancy should be planned in these patients during the period when remission is achieved with treatment. The risk for fetal and maternal complications is minimal in the periods when the disease becomes inactive with low-dose steroid treatment (31). In

addition, inflammatory myopathies may start during pregnancy or the postpartum period.

Familial Mediterranean Fever

Pregnancy does not have any influence on the course of this disease, its intensity, and duration of the attacks (32). However, because of recurrent episodes of peritonitis, infertility can occur because of pelvic adhesions (33). Abortion may occur during early pregnancy because of uterine contractions depending on abdominal pain attacks. Therefore, controlling acute episodes is very important. In addition to this, the risk of the premature rupture of membranes and prematurity is also high (32, 34). Besides deterioration in renal functions, the risk of abortion and dead birth increases in patients with amyloidosis (8, 35).

Antirheumatic Drug Use During Pregnancy and Breastfeeding

The US Food and Drug Administration (FDA) divided drugs into five main groups in terms of their effects on the fetus if used during pregnancy:

A: Drugs shown to create no risk on fetuses, with a sufficient number of studies on humans.

B: Drugs whose negative impact on fetuses cannot be shown in animal studies, without a sufficient number of studies on pregnant women.

C: Drugs whose negative impact on fetuses was shown in animal studies, without a sufficient number of studies on pregnant women. Despite potential risks, these drugs can be used in pregnant women considering the benefits to be obtained.

D: There is evidence of fetal risk in humans. If the absolute use of a drug is necessary, if there is no safer drug, and if there is a danger to life, it can be used.

X: Fetal anomalies in studies on humans or animals have shown and/or there is evidence of fetal risk in humans. Risks that will arise with the use of these drugs in pregnant women are more than the potential benefits.

Simple Analgesics: (Category B)

Paracetamol (acetaminophen) is the first preferred analgesic during pregnancy and lactation; it has been reported to rarely cause a decrease in birth weight.

Salicylates: (Categories C, D)

Salicylates have no adverse effects on fertility. Fetal anomalies and teratogenic effects have not been reported in studies. Low doses used for an antiplatelet effect are considered reliable. Usage over 3 g/day may result in a reduction in uterine contractility and prolongation in the duration of pregnancy and delivery. In those regularly using aspirin, an increase may occur in the risk for anemia and antepartum or postpartum bleeding. It may cause premature closure of the ductus arteriosus in the fetus. Full-dose usage at a time close to delivery may increase the risk of intracranial bleeding in the fetus by decreasing platelet aggregation. Therefore, it is not recommended to be used in the last 6–8 weeks of pregnancy in anti-inflammatory doses (36). Salicylates are in category C in doses below 150 mg/day and in category D in standard doses.

Non-steroidal Anti-inflammatory Drugs: (Categories B, C)

NSAIDs are agents that inhibit prostaglandin synthesis and uterine contractions and prolong the gestation period. They do not affect the ability to get pregnant, but usage at the time of fertilization may increase the risk of miscarriage. Short-acting agents such as ibuprofen, indomethacin, and diclofenac should be preferred during pregnancy. These drugs can cause complications such as a decrease in the gestation period as well as an increase in the risk of postpartum hemorrhage, premature closure of the ductus arteriosus, fetal intracranial hemorrhage, pulmonary hypertension, and renal dysgenesis. They should be discontinued 6–8 weeks before birth (36, 37).

Corticosteroids: (Category B)

Short-acting prednisone, prednisolone, and methylprednisolone are metabolized in the placenta; they pass to the fetus at a rate of approximately 10% (36). Therefore, they are often preferred in pregnant women during the exacerbation of rheumatic diseases. They are quite safe during pregnancy up to the dose of 15–20 mg/day, and the dose can even be increased to 60 mg/day. If long-term doses above 5–10 mg/day are administered, apart from the general side effects of steroids, the risks of gestational diabetes, hypertension, and premature rupture of membranes in mothers increase (36, 37). An increased risk of cleft palate has been reported with steroid usage in the first trimester (38). Premature deliveries may occur. Those using steroids at <20 mg/day for 6 months should be intravenously given a stress dose of 20–40 mg. Although it is not very common, adrenal suppression and infection of newborns should be carefully monitored (36). Hydrocortisone, cortisone, or prednisone should be preferred in pregnant women. Dexamethasone and betamethasone are included in category C because they reach similar maternal and fetal concentrations after passing through the placenta (37).

Disease-modifying Drugs (DMARDs)

Sulfasalazine: (Category B)

Sulfasalazine is a relatively safe drug during pregnancy, and it is recommended to be used together with folic acid. Although no negative effects have been reported on the fertility of women, it may lead to temporary infertility by causing a decrease in sperm count and quality in men. It crosses the placenta but does not lead to an increase in the risk of fetal morbidity and mortality (36, 37).

Chloroquine and Hydroxychloroquine: (Category C)

Chloroquine is not recommended because it causes congenital malformations. However, hydroxychloroquine is safe for pregnant women in low doses, and it does not show teratogenic effects. Hydroxychloroquine can be used in patients with SLE to decrease the risk of exacerbation and suppress the disease activity. As the half-life of 8 weeks is long, the fetus can stay under the influence of medication for several months despite drug cessation. If pregnancy is planned, the drug should be discontinued months prior; if there is pregnancy, the drug should be continued because the fetus will remain under the influence of the drug for several months

even after cessation. Hydroxychloroquine is not known to cause infertility (36, 39).

Colchicine: (Category D)

Colchicine is an alkaloid that can affect microtubule formation and thus adversely affect mitosis; it passes through the placenta. However, there are several case reports or retrospective studies showing that it can be safely used during pregnancy. A prospective study with a large number of patients and control group was conducted to evaluate the effects of the use of colchicine on the fetus during pregnancy (40). The results of 238 patients, 97% of who used colchicines in the first trimester, and 964 patients who did not use colchicine were compared. A statistically significant difference was not observed between the two groups in terms of miscarriage, stillbirth, and ectopic pregnancy rates. The major congenital anomaly rate was similar between both groups and similar to that of the general public. These results were found to be consistent with previous data; thus, colchicine was concluded to have no teratogenic effects on humans.

Methotrexate: (Category X)

Methotrexate inhibits purine synthesis; because it has teratogenic effects (e.g., anencephaly and meningomyelocele), its use during pregnancy is contraindicated. The risk is higher particularly with doses above 10 mg/week and when it is used between the sixth and eighth weeks of gestation. In higher doses, the risk of embryopathies such as cardiac defects, pulmonary atresia, craniosynostosis, and limb defects in the fetus increases. In cases when pregnancy is planned, the interruption of treatment at least three menstrual cycles prior to pregnancy and continuation of the use of folic acid during the entire pregnancy are required (36, 37).

Leflunomide: (Category X)

Because leflunomide inhibits pyrimidine synthesis, it is embryotoxic. Hence, effective contraception should be ensured during the period when the drug is used. The half-life of the drug is 14-15 days, and it may take 2 years to be cleared from the plasma. Therefore, it should be discontinued at least 2 years before pregnancy, and cholestyramine can be administered to accelerate the elimination of the drug. For this, 8 g of cholestyramine is given three times daily for 11 days, and the drug level is then controlled in the blood; if it is still high, it may be necessary to give more cholestyramine. After this treatment, the completion of at least three menstrual cycles before pregnancy should be ensured (36, 37).

Gold Salts

The adverse effects of gold salts on fertility have not been reported. They may cause toxicity after passing through the placenta and accumulating in the fetal liver and kidney. However, the enhancing effect of neonatal malformations has not been indicated (36). Because the elimination period is long during pregnancy, it will be more appropriate to use by decreasing and minimizing the dose instead of completely discontinuing the drugs. Nowadays, gold salts are not commonly used.

Cyclophosphamide: (Category D)

The regular daily use of cyclophosphamide leads to amenorrhea within a year and causes permanent infertility in >70% of patients. Effective contraception is needed because of its teratogenic effect during usage. The risk of congenital malformations is approximately 20%. It should be discontinued at least 3 months before pregnancy. In life-threatening cases, because it is relatively safer in terms of congenital anomalies, it can be used in the second and third trimesters (36, 37).

Azathioprine: (Category D)

Azathioprine has no adverse effects on fertility. It can cross the placenta but does not show teratogenic effects during the early stages of pregnancy because of the lack of an enzyme that converts it to the active metabolite in the fetal liver. When used during the entire pregnancy, intrauterine growth retardation, adrenal hyperplasia, decreased serum immunoglobulin levels, and chromosomal abnormalities have been reported. It should be used only in the presence of severe or life-threatening rheumatic diseases because of carcinogenesis and the risk of long-term immunosuppression. In this case, it is useful to decrease the dose of the drug in the 32nd week to avoid neonatal leukopenia and thrombocytopenia (36, 37).

Penicillamine: (Category D)

Penicillamine has been found to have teratogenic effects in animal studies and has been reported to cause connective tissue defects. Therefore, its use is not recommended during pregnancy. If a patient using it gets pregnant, the dose should gradually be tapered and the drug should be discontinued (36).

Cyclosporine: (Category C)

Unless necessary, it should not be used because of the risk of congenital malformations (36).

Biological Agents:

There are insufficient data on their effects on pregnancy. Studies on animals have shown that although fetal exposure to biological agents is little in the period of organogenesis, it gradually increases and reaches levels close to the maternal concentration during the second trimester. The American College of Rheumatology did not make any specific recommendations on the use of biological agents in pregnant women because of inadequate and contradictory data (41).

TNF inhibitors: (Category B)

TNF inhibitor usage during pregnancy is controversial. Because randomized controlled studies on this subject cannot be conducted, suggestions are based on expert opinions or retrospective patient and case records. They are generally not recommended during pregnancy. In a study where >120,000 side effects obtained from the FDA database were examined (42), a total of 61 congenital anomalies were identified in 41 children born to pregnant women, 22 of whom used etanercept and 19 of whom used infliximab. One or more anomalies associated with VACTERL syndrome (vertebral anomalies, anal atresia, cardiac defects, transesophageal, and renal and limb anomalies) were found in 59% of children, and it was concluded that it

could be a possible side effect of the TNF inhibitor. However, later, in another study conducted using community-based data (43), the incidence of VACTERL syndrome in those using TNF inhibitors has been reported to be similar to that in the general population.

Infliximab: Measurable levels of active ingredients were not observed in the serum of infants and maternal milk of three Crohn's patients in whom infliximab treatment was applied at 5 mg/kg in regular intervals until the 30th week of pregnancy and 3–14 days after birth (44). However, when used after the 30th week, it was seen at a high level in the blood of newborns (45).

Etanercept: No significant anomalies were found in the result of its use in pregnant women with RA (46). When the amount of drug was measured in the baby and breast milk after birth, etanercept was not detected in the blood of 3-month infants fed with this milk, despite the low concentration in breast milk (47).

Adalimumab: A Crohn's patient using adalimumab until the 30th week of pregnancy gave birth to a healthy baby. However, 6 days after the medication administered because of disease exacerbation, it was determined that the level of drug increased in milk (48).

Certolizumab: Transplacental transition is minimal. In pregnant women exposed to certolizumab, no harmful effect was determined during pregnancy when compared with healthy controls (49).

Golimumab: In a study conducted on animals, it was indicated that usage during pregnancy does not lead to miscarriage, stillbirth, or developmental morphological anomalies in newborns, and no adverse effects the immune system were reported (50). Because it is a relatively new drug, data on its reliability are limited. Congenital anomalies were detected in only 1 of 40 patients using golimumab during pregnancy. It has been reported that spontaneous miscarriage took place in 13 patients and that 30.8% of them were simultaneously using methotrexate (51).

According to the records of >2000 pregnant women exposed to TNF inhibitors in the first trimester, an increase in the risk of miscarriage, low birth weight, prematurity, and congenital anomalies are not mentioned. However, their exact long-term effects are unknown, and the risks of immune response degradation and infection in newborns and infants exist. Thus, TNF inhibitors are recommended to be discontinued during pregnancy. If maternal disease requires the use of these drugs during pregnancy, they should be discontinued prior to the 30th week. In addition, because the half-life of these drugs is long, live vaccines should not be given to infants within the first 6 months (49).

Rituximab: (Category C)

Although it seems reliable in the early stages of pregnancy, because usage in the second and third trimesters causes B-cell depletion in the fetus and the long-term effects of this condition are unknown, it is not recommended for use during pregnancy. As it has a long half-life, it is required to be discontinued 6 months before pregnancy (49). According to the global drug safety data, 90 of 153 women getting pregnant while using rituximab gave live births, 33 suffered spontaneous miscarriage and 28 had to undergo therapeutic termination of pregnancy. Of the live births, 24% were premature. Neonatal death or congenital anomalies did not occur in the babies of 21 patients who continued to use the drug during pregnancy. Mild and self-healing hematologic disorders developed in 11 infants, and an infection developed in four infants (52).

Abatacept: (Category C)

It crosses the placenta. Discontinuation is recommended 3 months before pregnancy (45).

Anakinra:

As it has a short half-life of 4–6 h, there is no need for cessation before pregnancy, but it is not recommended during pregnancy (49). It has been reported that three patients with adult-onset Still's disease who continued the use of anakinra during pregnancy had healthy children (53, 54).

Tocilizumab:

No evidence showing teratogenic/dysmorphic effects was found in animal studies (55). In case series with RA patients in whom tocilizumab monotherapy or combination therapy was applied, apart from elective and spontaneous miscarriages, approximately half the patients gave birth to healthy babies. However, cessation has been suggested 3 months before pregnancy because of insufficient data (49).

Drug use during lactation is summarized as follows (36, 37):

The most reliable analgesic is paracetamol. It passes into breast milk in a very small amount. Salicylates also pass into breast milk at levels as low as 4%–8% of the maternal dose. Continuous low-dose aspirin can cause Reye's syndrome by accumulation of the drug in the tissues of the baby. Among NSAIDs, the ones with a high molecular weight and those substantially binding to protein hardly pass into milk. The ones with a long half-life of plasma remain longer in milk. Naproxen and ibuprofen pass into milk at very lows levels, and diclofenac and fenbufen have a short half-life. These drugs can be safely used during breastfeeding. Despite having a long half-life, piroxicam can be safely preferred because a little amount passes into milk. Indomethacin is not recommended because it can lead to convulsions in infants. Most NSAIDs can increase the risk of kernicterus by displacing bilirubin; therefore, in newborns with jaundice, NSAID usage by the mother is contraindicated. Prednisone and prednisolone as corticosteroids are reliable up to a 40 mg daily dose. Only 0.3% of maternal prednisone dose passes into breast milk. To ensure less passage into milk, breastfeeding of the baby should be preferred 4 h after taking the drug. Sulfasalazine passes into milk at a rate of 40%–50%, but it can be used during lactation because it does not cause adverse effects in infants. Hydroxychloroquine should be used with caution only when extremely necessary, considering its potential of accumulation in infants and the low elimination rate. Although gold salts pass into milk in trace amounts, it creates a risk for the baby because of long-time accumulation and should therefore be avoided. Methotrexate, leflunomide, D-penicillamine, aza-

thioprine, cyclosporine, and cyclophosphamide should not be used during lactation. Although data are insufficient concerning the use of biological agents during breastfeeding, usage seems safe. However, further studies are needed on this topic.

Conclusion

In the presence of rheumatic diseases, it is important to keep disease activity under control prior to pregnancy and inform mothers about potential complications. It should be kept in mind that patients should be closely followed in terms of disease exacerbations during pregnancy and probable fetal and maternal complications in a multidisciplinary way; in addition, if necessary, an appropriate treatment plan is required to be made. Moreover, it is important to train patient on exacerbations that may occur in the postpartum period and call for checks at regular intervals. In this process, to keep disease activity under control and to suppress the occurring exacerbation, it will be appropriate to decide which rheumatic drugs to use, considering the risk–benefit ratio in light of scientific data.

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