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Fertility and pregnancy outcomes in patients with immune-mediated rheumatic diseases

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ABSTRACT

Impaired fertility is an important public health concern, especially in patients with immune-mediated rheumatic conditions. Frequency of infertility /subfertility vary among rheumatic diseases – higher in systemic lupus erythematosus or rheumatoid arthritis, than in other autoimmune diseases. Risk factors like age, nulliparity, disease activity or medication such as NSAIDs, corticosteroids, cyclophosphamide are mostly encountered. Treating a pregnant woman is a challenge: the well-being of mother and child has to be considered, as tight disease control before, during pregnancy and postpartum is mandatory to minimize adverse outcome risk. Safety of biological therapies during preconception, pregnancy, and postpartum is crucial, anti-TNFs being safe in early pregnancy, second, but not third trimester. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage. Concerning the child, live-attenuated vaccines are to be avoided for the first 6 months of life due to persistence of biologics.

Keywords: rheumatic conditions, systemic lupus erythematosus, fertility, pregnancy, obstetrical outcome, autoantibodies

FERTILITY IN IMMUNE-MEDIATED RHEUMATIC DISEASES (RMD)

Impaired fertility is an important public health concern as it affects 9% of the general population and around 25-42% of the patients with rheumatoid arthritis (RA), when looking at the people with auto-immune rheumatic conditions (1). Of women interested in having children, 55% with RA and 64% with systemic lupus erythematosus (SLE) had fewer children than originally planned.

Infertility is defined as the "failure to achieve a clinical pregnancy after 12 months or more of regular unprotected intercourse" while subfertility is "a delay in achieving pregnancy" as the capacity for fertility may be diminished, not necessarily absent (2).

On the other hand, time to pregnancy is a reliable way to measure fertility and vary among rheumatic musculoskeletal diseases (RMD), being higher in SLE and RA than in the other autoimmune diseases.

Fertility in SLE may be affected either by the presence of specific autoantibodies as well as by utilized therapeutic agents (3). Pregnancy in SLE patients entails an increased risk for both maternal and fetal complications such as disease flare, preeclampsia, miscarriages and preterm labors or fetal loss, intrauterine growth restrictions, neonatal lupus. Physicians should expect optimal outcomes if the disease showed no signs of activity six months prior to conception or during pregnancy interval (4).

During pregnancy, differentials should be promptly made between physiological changes that occur, disease flares and preeclampsia in order to determine the correct treatment and management.

A study published in 2012 evaluated a cohort of patients with rheumatoid arthritis (RA) and SLE to assess the effects of infertility, pregnancy loss, and patient concerns on family size. Results showed that more than half of patients who were diagnosed prior to accomplishing childbearing had fewer chil-

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dren than they had originally planned. Contributing factors are pregnancy loss in women with SLE and patient concerns about the impact of rheumatic disease on children and family life (1).

FACTORS INVOLVED IN THE IMPAIRED FERTILITY IN SLE AND RA

SLE patients account for 1% of infertile patients, knowing that worldwide infertility rate is estimated at 9%. There is a drastic decrease of pregnancy rate once the diagnosis of SLE has been set and it may vary depending on ethnicity. Patients with SLE have a more reduced family size than the healthy population.

Aging is a global reason leading to declined fertility through a loss in ovarian reserve and a poor remaining oocyte quality. Women with SLE might exhibit a delay in conceiving since physicians advise them to have a six-month free interval of disease activity and after medication adjustments are made to suit pregnancy safety. Sometimes age can participate to the inability of SLE patients to conceive or to maintain the pregnancy to term (5).

There are several factors that contribute to impaired fertility including drug toxicity and specific autoantibodies (3).

SLE patients can encounter menstrual disturbances and irregularities as a consequence of medications such as high-dose corticosteroids, non-steroidals or cyclophosphamide or due to disease activity. Pasoto et al. revealed that patients with high disease activity, exhibiting a SLEDAI score over 8 are more prone to developing menstrual disturbance than those with less intense disease, associating no additional hormonal disturbances (6).

Subfertility can be attributed to co-existing conditions like autoimmune thyroiditis, endometriosis, genital inflammation or infections. Due to immunosupressive therapies, SLE patients have a higher risk of contracting vaginal infections. Subfertility can also be caused by SLE complications like renal involvement, chronic renal insufficiency or secondary antiphospholipid syndrome (7).

SLE patients that have chronic kidney disease due to lupus nephritis might develop fertility issues through hypothalamic-pituitary malfunction, with erectile dysfunction or menstrual disturbances.

Secondary antiphospholipid syndrome (APS) can affect around 30% of SLE patients and be responsible for spontaneous abortions, stillbirth or premature delivery, as well as thrombotic events. However, APS can also influence fertility during fertilization or implantation process (8).

Some SLE patients suffer from premature ovarian failure (POF) related to gonadal toxicity of medications, mainly cyclophosphamide or attributed to the disease. POF is defined by early amenorrhea (over 4 to 12 months) with increased levels of circulating FSH and low estrogen levels under the age of 40.

Altered infertility was also mentioned in SLE male patients, apparently linked to testis damage from the disease. A study published by Soares et al. indicated there is a destruction of the seminiferous tubules leading to a reduction of testis volume and sperm abnormalities (9).

In RA, many female patients wanting to conceive have a time to pregnancy of more than 12 months; also, the disease RA is often undertreated meanwhile, so it may be active for a long amount of time. A nationwide prospective study on pregnancy (PARA study), which included women preconceptionally or in the first trimester of pregnancy, evaluated the association of disease characteristics and medication use with the time needed to obtain a pregnancy. Data from the study concluded that 42% of the patients needed more than 12 months until conception. Furthermore, higher disease activity (almost 75% of the patients with active disease, DAS28 > 5.1 during the first year) did not achieve pregnancy in the first year.

Age, nulliparity, disease activity and medications are the most encountered risk factors (10).

Tight control of the disease before pregnancy remains an important factor in the planning of the pregnancy as it leads to improved pregnancy outcomes.

About 50% of pregnancies are unplanned and many women are already taking medications when they become pregnant that may not be compatible with pregnancy (11,12) (such as cyclophosphamide, metothrexate or leflunomide, NSAIDs). Other factors with impact on fertility in patients with RMD include partnership difficulties arising from the disease-related stress, physical and emotional problems that are associated with decreased sexual interest and functioning, concerns about the pregnancy that might cause RMD exacerbation and also concerns about the adverse effects of the disease itself on the care-giving capacity of the mother.

DRUG-INDUCED FERTILITY ISSUES

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis, causing luteinized unruptured follicle syndrome (LUF) with a defective oocyte release, thus participating to infertility (13). LUF syndrome can resolve once medication is withdrawn (3).

Glucocorticoids (GLC) act on the hypothalamic-pituitary-gonadal hormonal axis, causing defective production of follicle stimulating hormone (FSH) (13). The impact of prednisone use was dose dependent, with significantly longer time to pregnancy when daily dose is above 7.5 mg predniso-

lone. Other factors as smoking, duration of the disease, rheumatoid factor or ACPA antibodies, the use of methotrexate or sulfasalazine didn't interfere with the time to conception (14).

Cyclophosphamide (CYC) has a gonadotoxic effect dependent on the cumulative dose and patient's age. A cumulative dose of over 10 grams has an increased risk for depletion of ovarian oocytes, leading to substantial decrease in anti-Mullerian hormone (AMH) and ovarian failure (4). Lower doses have also been proven harmful and associate premature menopause at ≥ 35 years old. After CYC interruption, SLE patients might recover and have normal menstrual cycles and conceive without the risk of fetal abnormalities. Current recommendations state to delay conception with at least three months from the last administration, to lower the risk of teratogenicity. Mycophenolate mofetil (MMF) is an available option for young, childbearing patients.

Spermatogenesis can also be affected by CYC treatment and published data indicate a reduction in sperm quantity and quality and lower testosterone levels.

Methotrexate can cause miscarriages in patients exposed to it during the first trimester of pregnancy but apparently it has no effect on AMH levels or ovarian reserve (15).

There are several factors that contribute to impaired fertility including complications of the disease, drug toxicity, co-existing conditions or specific autoantibodies (3).

SLE patients can encounter menstrual disturbances and irregularities as a consequence of medications such as high-dose corticosteroids, non-steroidal drugs or cyclophosphamide or due to disease activity. Pasoto et al. revealed that patients with high disease activity, exhibiting a SLEDAI score over 8 are more prone to developing menstrual disturbance than those with less intense disease, associating no additional hormonal disturbances (6).

IMPORTANCE OF A PLANNED PREGNANCY IN PATIENTS WITH RMD

A study published in 2012 evaluated a cohort of patients with rheumatoid arthritis (RA) and SLE to assess the effects of infertility, pregnancy loss, and patient concerns on family size. Results showed that more than half of patients who were diagnosed prior to accomplishing childbearing had fewer children than they had originally planned. Contributing factors are pregnancy loss in women with SLE and patient concerns about the impact of rheumatic disease on children and family life (1).

Pregnancy in SLE

While planning a pregnancy in SLE patients, the disease should be quiescent at least six months before conception. The risk of maternal and obstetrical complications increase if an active disease is present at the time of conception (16). An observational study on 385 pregnant SLE patients with inactive or mild-moderate disease at time of conception found that 81% of patients had uncomplicated pregnancies (17), while a published study on 267 pregnant SLE patients found that women suffering from high disease activity in the first two trimesters had a three-fold higher risk of fetal loss compared to patients presenting an inactive or low disease activity (18).

Pre-conception evaluation

The pre-conception evaluation should include the assessment of major organ function and disease activity. Necessary information includes a detailed obstetrical history (miscarriage, preeclampsia, small for gestational age fetus, preterm birth and stillbirth), to identify a hypercoagulability status or any other maternal condition that may affect pregnancy outcome (19). Routine preconception laboratory evaluation is mandatory SLE patients as is in the healthy population as well as to specific tests. Rheumatologists should request autoantibody profile that might increase maternal of fetal risks such as antiphospholipid and anti-Ro antibodies.

Nevertheless, physicians should review patients' medications and adjust it to attain disease control while administering pregnancy-safe agents.

Pregnancy should be contraindicated if patients suffer from severe pulmonary hypertension or restrictive lung disease, advanced renal insufficiency or heart failure and previous severe (pre)eclampsia or hemolysis, elevated liver enzymes, low platelet count (HELLP) despite therapy (20).

Pregnancy can be deferred if patient has had a disease flare in the last six months, current active lupus nephritis or stroke in the last half year.

In high risk patients careful monitoring in a multidisciplinary approach is necessary (19) and surrogacy or adoption should be considered an option if a natural pregnancy is not feasible.

Autoantibodies related to fertility issues

Antiphospholipid antibodies, namely lupus anticoagulant, anti-beta2-glycoprotein 1, anti-cardiolipin antibodies have been reported in SLE patients, ranging from 20% to 60%. They are also present in antiphospholipid syndrome (APS) that may be independent of SLE (primary APS) or associated to SLE (secondary APS) (3). Antiphospholipid antibodies seem to interfere with endometrial decidualization, leading to a damaged implantation (21). Another

study published in 2016, conducted on 351 infertile patients searched whether there is an association between the presence of specific autoantibodies and AMH levels and found that 14.2% of patients with at least one positive antiphospholipid antibody had decreased AMH levels (8).

Apart from the above-mentioned factors that might affect fertility in SLE, there are other factors worth mentioning, such as partnership hardships arising from the chronic disease-related stress, physical and emotional problems associated with decreased sexual interest and functioning, concerns on the risk of disease exacerbation during pregnancy or on the impairment brought on by the chronic illness and the capacity of the mother to care for the offspring (4).

Fertility preservation methods represent an option in SLE patients requiring cytotoxic drugs but are relatively difficult to access in dedicated centers. Gonadotropin-releasing hormone analogues (GnRH-a) can prevent POF but data is scarce on pregnancies in SLE after this treatment. However, it is recommended to be administered prior to or during CYC treatment.

Assisted reproduction methods like in vitro fertilization are thought to be safe in SLE population. Patients with associated APS are recommended to initiate low-dose aspirin (LDA) or low-molecular weight heparin (LMWH) during pregnancy depending on individual risk profile (3).

Limited data are available on fertility preservation methods in menstruating women with SLE who require treatment with alkylating agents. Cryopreservation of ovarian tissue or oocytes/embryos are poorly investigated options and require specialized centres, which may not be easily accessible.

The most extensively studied method for POF prevention in patients with SLE involves gonadotropin-releasing hormone analogues (GnRH-a), with a good safety and efficacy profile.

GnRH-a have been efficacious in patients with cancer.

Monitoring pregnancy in SLE

Managing SLE pregnancy requires close monitoring of a multidisciplinary team, including a rheumatologist and an obstetrician. If patient is considered at high risk, monitoring visits are more frequent to examine both mother and fetus. Each follow-up visit includes detailed physical examination, routine and specific laboratory tests and investigations, according to the individual risk profile of each pregnancy (19).

Usually, the rheumatologist should assess patient every four to six weeks or more frequently if there is a suspicion of active disease or acute flare and the obstetrician should evaluate the patient monthly until week 20 of pregnancy, then every two weeks until week 28 and weekly onwards.

Special monitoring situations include the presence of high titer anti-Ro antibodies which require fetal echocardiography weekly between weeks 16-26 and every 2 weeks onwards, continued upon delivery. If pre-eclampsia occurs, uterine artery Doppler and fetal umbilical artery Doppler velocimetry should be intensified. In case of intrauterine growth restriction, there is a need to increase the frequency of growth monitoring by ultrasound and fetal surveillance tests (18).

Monitoring SLE activity

Normal pregnancies have physiological changes like mild thrombocytopenia, mild anemia, elevated erythrocyte sedimentation rate (ESR), and mild range proteinuria (< 300 mg/24 h). A normal increase in complement level (up to 50%) is seen in pregnancy and may conceal disease activity. These changes should be carefully distinguished from an acute SLE flare or underlying maternal pathology like preeclampsia, thus individual assessment of each patient in association with the clinical picture is mandatory for optimal management for. Changes in therapy solely for serologic findings is not recommended (19).

Postpartum monitoring

SLE patients that present with active disease at time of conception or with severe organ damage have a higher risk of developing postpartum SLE flare when compared to patients with inactive disease (22). Laboratory tests are to be performed one month post uncomplicated delivery and should include urinalysis, urine protein/urine creatinine ratio; complete blood count. Antibody titer and complement levels (CH50, or C3 and C4) should also be measured (1).

Pregnancy in RA

Pregnancy planning is an important part of the doctor-patient discussion, with RA being prevalent in women of childbearing potential. For many patients, the activity of the disease improves during pregnancy, the therapeutic challenge consists in choosing the medication with minim fetal toxicity, while maintaining the low activity of the disease.

There is an influence on fertility and pregnancy, in terms of disease as well as medication: fertility is impaired and the time to pregnancy is increased; Cyclophosphamide treatment affects fertility in both women and men.

The effect of pregnancy on the disease

RA activity diminishes starting with the first trimester and remains so during pregnancy, and will increase in the first months postpartum; however, joint pain or functionality may be exacerbated in relation to pregnancy changes (23).

The risk of new diagnosed RA is low during pregnancy (whether it is the first pregnancy or not) and higher in the first 3 to 12 months postpartum (especially after the first pregnancy) compared to other time frames. On the other hand, symmetrical inflammatory arthralgias, carpal tunnel syndrome, increased ESR, or hepatocytolysis syndrome, are changes that frequently accompany pregnancy and may require differential diagnosis with RA activity.

The obstetrician monitors the pregnancy in accordance with the monitoring guidelines, pregnancy complications, gestational diabetes, preeclampsia. Increased attention requires cervical damage, the risk of atlanto-axial subluxation in patients requiring orotracheal intubation;

The effect of RA on pregnancy

Patients with RA have a higher risk of pregnancy complications, abortion or perinatal death compared to healthy pregnant women. However, rigorous monitoring before and during pregnancy leads to a significant decrease of this risk, which becomes within this subgroup, comparable to that of the general population. Data from a retrospective observational study of 433 patients in their first pregnancy show a 40% reduction in the risk of pregnancy complications and a 60% reduction in the risk of abortion or perinatal death, compared between groups of patients with and without optimal monitoring of disease and pregnancy (5).

The risk of obstetric events is increased by hypertension, intrauterine growth restriction and cesarean delivery but not by fetal morbidity or fetal death. A large study shows that patients with RA have a 2 times higher risk of high blood pressure and preeclampsia compared to patients with AS or the general population (24).

PREGNANCY OUTCOMES OF COUPLES EXPOSED TO BIOLOGIC DRUGS

Biological agents have radically changed the prognosis of rheumatic diseases, but treating a pregnant woman is a challenge, as the well-being of mother and also of the child has to be considered.

On the other hand, the tight control of the disease before and during pregnancy and postpartum is mandatory in order to minimize the adverse outcome risk.

Concerning the biological agents, it is important to know data about the safety before, during pregnancy and postpartum, also the rate of pregnancy loss, congenital malformations, also the long term complications due to in utero exposure to these agents.

When treating a pregnant patient with RMD with biologics, there are certain points that need to be considered: the structure of the drug and the risk of passing the placenta, when or if the biologic should be discontinued during pregnancy, and the long-term effects on neonate. On the other hand, the maternal disease flare or active disease is well-known to be related to poor outcome and preterm delivery (25).

Biologics are derivatives of IgG and differ in structure, half-life, and placental passage. During the first trimester due to its size, the IgG antibodies do not cross the placenta (passive diffusion). In the second trimester, maternal antibodies are actively transported across the placenta by the neonatal Fc receptor (FcRn), so treatment of mother with IgG antibodies expressing high affinity to fetal Fc receptor can lead to increased levels of biologics in fetal blood from the second trimester until delivery (26,27).

During the second and third trimester, fetal IgG1 levels reach 50% of maternal levels at 28–32 weeks' gestation and increase exponentially afterward with maximal transfer in the final 4 weeks prior to delivery. At delivery, cord blood levels of neonates exposed to some biologics in late gestation are often much higher than maternal serum drug levels. This depends on the moment of gestation in which the drug was used (the later in pregnancy, the higher the cord drug levels), the half-life of the drug (the longer its half-life, the more likely its passage across the placenta), and the structure of the Fc receptors. Biologics with modified Fc receptors (e.g. etanercept) or those lacking an Fc portion (e.g. certolizumab) are less efficiently transported across the placenta and can be used throughout pregnancy or at least until 34 weeks gestation (e.g. etanercept) (28).

Studies show that among anti-TNFα agents etanercept has a shorter half-life and less binding to placental Fc receptors than infliximab and adalimumab. In the case of certolizumab pegol (pegylated anti-TNFα agent), active placental transport is not thought to occur.(27).

Regarding IL-1 inhibitors, data from the studies show that women exposed to canakinumab during pregnancy had no congenital abnormalities and a single early miscarriage occurred at six weeks' gestation in a woman with refractory Cogan's syndrome. Also, 23 women and 6 men were exposed to anakinra with a single case of renal agenesis and ectopic neurohypophysis with growth hormone deficiency noted in an infant whose mother was treated from 9 weeks' gestation till delivery. Cases of

rilonacept use during pregnancy have yet to be published (28).

In respect to IL-6 inhibitors, out of 358 observed pregnancies with tocilizumab the miscarriage rate was 23% and elective termination of pregnancy 18.4%; the livebirth rate was 60%. Studies on sarilumab use in pregnancy have yet to be published.

In patients treated with IL-17A inhibitors, the 66 pregnant women received secukinumab and there were 12.1% were miscarriages, 48% patients had an elective termination of pregnancy, 22% were livebirths (without any congenital malformation), and 16% ongoing pregnancies; no information was provided on 18 pregnancies with paternal exposure (28).

Of 18 pregnancies on ixekizumab, 44.4% were livebirths and 27.8% were miscarriages or elective terminations. One-third of cases (n = 6) had no recorded outcome and no congenital malformations were reported. Of the 34 cases with paternal exposure to ixekizumab, the vast majority (82.4%) resulted in livebirths. Also, 63 pregnancies with exposure to ustekinumab within three months pre-conceptually or in the first trimester were included in the study and the livebirth rate was 57.1%, and miscarriage was low at 15.9%.

In one open-label study on belimumab, a total of 13 pregnancies in 13 patients were included and the median number of treatment courses with belimumab (400 mg per dose) was two. During the study, there were 11 live births (84.6%), one episode of omphalitis in one fetus who recovered well with antibiotic treatment, and no fetus had leukopenia, lymphopenia, or thrombocytopenia in the days after birth. No fetal anomalies were found in this series. Of six patients with a history of recurrent pregnancy loss, four had live births. Thus, it was concluded that there was no increase in the risk of fetal anomalies or severe infection in the patients exposed to belimumab during pregnancy (29).

The pregnancy and child safety in couples with males with SpA exposed to long-term TNFα inhibitors was positive according to some studies (30).

According to EULAR Points to Consider For Use of Antirheumatic Drugs in Pregnancy, among bDMARDs, the continuation of anti-TNFs during the first part of pregnancy should be considered and it is advised to be stopped before the twentieth week of pregnancy. Certolizumab pegol may be considered for use throughout pregnancy due to the low rate of transplacental passage; ETA advised to be stopped in the 32nd week of pregnancy. BDMARDs (e. g. RTX, ANA, TOC, ABA, BEL, and UST) have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control the maternal disease (31).

Regarding vaccination in newly-born baby of the mothers who received biologic therapy, it needs to be taken into account that, if a biologic has been continued beyond 28 weeks, the exposed neonate has higher drug levels of drug in the cord than maternal serum drug levels. There are specific measures that have to he considered for the child, like avoidance of live vaccines (e. g. rotavirus, BCG) for the first six-seven months because of the ineffective clearance by the neonate's immature RE with the persistence of detectable drug levels in the infant's serum for 6-7 months. On the other hand, all the other non-live vaccines are safe to be administered (31).

CONCLUSIONS

The frequency and severity of infertility/subfertility vary among rheumatic diseases, being higher in SLE, RA. Also, there are many factors involved in subfertility like age, disease activity, medications.

The safety of biological therapies during preconception, pregnancy, and postpartum is crucial in inflammatory rheumatic diseases. Anti-TNFs agents appear to be safe in early pregnancy, second, but not the third trimester and etanercept and certolizumab may be considered for use throughout pregnancy due to the low rate of transplacental passage and no increased risk of congenital malformations. There is limited documentation on safe use in pregnancy for rituximab, tocilizumab,abatacept, belimumab and ustekinumab. No impact of some biologics (TNFi, RTX) was observed on male fertility and pregnancy outcome. It is recommended that live-attenuated vaccines be avoided in clinical practice for the first 6 months of life due to the persistence of biologics. To optimize management of RMD patients wishing to conceive, planning the process is essential within a multidisciplinary approach, including a rheumatologist and a gynecologist, explaining potential risks and available options if natural conception is no longer possible.

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REFERENCES

1. Clowse MEB, Chakravarty E, Costenbader KH, Chambers C, Michaud K. Effects of infertility, pregnancy loss, and patient concerns on family size of women with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Care Res* (Hoboken). 2012;64(5):668-74.

2. Practice Committee of the American Society for Reproductive Medicine. Definition of „infertility". *Fertil Steril.* 2006 Nov;86(5 Suppl 1):S228.
3. Khizroeva J, Nalli C, Bitsadze V, Lojacono A, Zatti S, Andreoli L, Tincani A, Shoenfeld Y, Makatsariya A. Infertility in women with systemic autoimmune diseases. *Best Pract Res Clin Endocrinol Metab.* 2019 Dec;33(6):101369.
4. Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis.* 2017 Mar 1;76(3):476-85.
5. Gayed M, Gordon C. Pregnancy and rheumatic diseases. *Rheumatology* (Oxford). 2007 Nov;46(11):1634-40.
6. Pimentel-Quiroz VR, Bertoli AM, Ugarte-Gil MF, Alarcón GS. Preconception, pregnancy, and lactation in systemic lupus erythematosus patients. *Rev Colomb Reumatol.* 2021 Jul.
7. Hickman RA, Gordon C. Causes and management of infertility in systemic lupus erythematosus. *Rheumatology.* 2011 Sep;50(9):1551-8.
8. Vega M, Barad DH, Yu Y, Darmon SK, Weghofer A, Kushnir VA, Gleicher N. Anti-mullerian hormone levels decline with the presence of antiphospholipid antibodies. *Am J Reprod Immunol.* 2016 Oct;76(4):333-7.
9. Costa M, Colia D. Treating infertility in autoimmune patients. *Rheumatology* (Oxford). 2008 Jun;47 Suppl 3:iii38-41.
10. Nordgren B, Fridén C, Demmelmaier I, Bergström G, Opava CH. Long-term health-enhancing physical activity in rheumatoid arthritis - The PARA 2010 study. *BMC Public Health.* 2012 Jun 1;12(1):1-10.
11. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol.* 2020;72(4):529-56.
12. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* (Hoboken). 2012 May;64(5):625-39.
13. Micu MC, Micu R, Ostensen M. Luteinized unruptured follicle syndrome increased by inactive disease and selective cyclooxygenase 2 inhibitors in women with inflammatory arthropathies. *Arthritis Care Res.* 2011;63(9).
14. Brouwer J, Hazes JMW, Laven JSE, Dolhain RJEM. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. *Ann Rheum Dis.* 2015 Oct 1;74(10):1836-41.
15. Hill MJ, Cooper JC, Levy G, Alford C, Richter KS, DeCherney AH, Katz CL, Levens ED, Wolff EF. Ovarian reserve and subsequent assisted reproduction outcomes after methotrexate therapy for ectopic pregnancy or pregnancy of unknown location. *Fertil Steril.* 2014 Feb;101(2):413-9.
16. Kwok LW, Tam LS, Zhu TY, Leung YY, Li EK. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. *Lupus*. 2011 Jul;20(8):829-36.
17. Buyon JP, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of pregnancy outcomes in patients with lupus: A cohort study. *Ann Intern Med.* 2015 Aug 4;163(3):153-63.
18. Clowse MEB, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum.* 2005 Feb;52(2):514-21.
19. Lateef A, Petri M. Managing lupus patients during pregnancy. *Best Pract Res Clin Rheumatol.* 2013 Jun;27(3):435-47.
20. Lockshin MD, Kim M, Laskin CA, Guerra M, Branch DW, Merrill J, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum.* 2012 Jul;64(7):2311-8.
21. Blank M, Cohen J, Toder V, Shoenfeld Y. Induction of anti-phospholipid syndrome in naive mice with mouse lupus monoclonal and human polyclonal anti-cardiolipin antibodies. *Proc Natl Acad Sci U S A*. 1991 Apr 15;88(8):3069-73.
22. Andrade RM, McGwin G Jr, Alarcón GS, Sanchez ML, Bertoli AM, et al.; LUMINA Study Group. Predictors of post-partum damage accrual in systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (XXXVIII). *Rheumatology* (Oxford). 2006 Nov;45(11):1380-4.
23. Yasmeen S, Wilkins EE, Field NT, Sheikh RA, Gilbert WM. Pregnancy outcomes in women with systemic lupus erythematosus. *J Matern Neonatal Med*. 2001 Apr 1;10(2):91-6.
24. Giles I, Yee CS, Gordon C. Stratifying management of rheumatic disease for pregnancy and breastfeeding. *Nat Rev Rheumatol.* 2019 Jul;15(7):391-402.
25. Limaye MA, Buyon JP, Cuneo BF, Mehta-Lee SS. A review of fetal and neonatal consequences of maternal systemic lupus erythematosus. *Prenat Diagn.* 2020 Aug 1;40(9):1066-76.
26. Baek HJ, Park E-J, Kim H, Jung M, Sung Y-K, Joo Baek H, et al. The Use of Biological Disease-modifying Antirheumatic Drugs for Inflammatory Arthritis in Korea: Results of a Korean Expert Consensus. *J Rheum Dis.* 2019 Dec 31;27(1):4-21.
27. Rath T, Baker K, Pyzik M, Blumberg RS. Regulation of immune responses by the neonatal fc receptor and its therapeutic implications. *Front Immunol.* 2015 Jan 5;5:664.
28. Soh MC, Moretto M. The use of biologics for autoimmune rheumatic diseases in fertility and pregnancy. *Obstet Med.* 2020 Mar 1;13(1):5-13.
29. Kao JH, Lan TY, Lu CH, Cheng CF, Huang YM, Shen CY, et al. Pregnancy outcomes in patients treated with belimumab: Report from real-world experience. *Semin Arthritis Rheum.* 2021 Oct 1;51(5):963-8.
30. Micu MC, Ostensen M, Bojincă V, Şerban O, Mihai M, Suţa C, et al. Pregnancy Outcomes in Couples with Males Exposed to Longterm Anti-tumor Necrosis Factor- α Inhibitor Therapies: A Prospective Study. *J Rheumatol.* 2019 Sep 1;46(9):1084-8.
31. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis.* 2016 May;75(5):795-810.