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Lupus nephritis in pregnancy; a mini-review to current knowledge

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Abstract

Systemic lupus erythematosus (SLE) is an auto-immune disease with the highest incidence in women of reproductive age. Recent studies indicate an increased rate of lupus flare during pregnancy. One main cause of death in lupus patients is renal involvement that is manifested as lupus nephritis. Active lupus nephritis is the biggest threat to pregnancy outcome in women with lupus. Consultation with a nephrologist, rheumatologist and perinatologist is recommended in order to carry a successful pregnancy to term.

Mini-Review

Implication for health policy/practice/research/medical education:
Recent studies indicated that high incidence of lupus occurs in women of childbearing age. Lupus and pregnancy have undesired reciprocal effects on one another. Lupus nephritis is one of the most hazardous manifestations of SLE during pregnancy. A tight control for these patients should be performed before, during, and after pregnancy.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects various organs. The highest prevalence is in women of reproductive age. In the United States, about 4,500 pregnancies per year occur in women with SLE (1). Lupus exacerbation in pregnancy can be observed in more than 50% of cases. In this mini-review we sought to review the recent investigations regarding lupus nephritis.

The flare of the disease occurs alike throughout the pregnancy and often occurs immediately after the termination of pregnancy (2). Changes in sex hormones during pregnancy affect the immune system and can cause SLE flaring (3). The immune cells and lymphatic tissues have receptors for sex hormones and the hormonal system has also receptors for cytokines. In pregnancy, serum levels of gonadotropins and sex steroids including luteinizing hormone and follicular stimulatory hormones, estrogen, and progesterone are different in people with SLE than in healthy ones (4,5). Within pregnancy in people with SLE, a decrease in serum concentrations of estradiol, cortisol, testosterone, and dehydroepiandrosterone sulfate and progesterone was reported in comparison with the control group (6). Some studies have identified the role of estrogen in the development of the disease. Estrogen can stimulate the maturation of peripheral immune cells, especially T cells. These cells contribute to promoting the immune system tolerance as well as the immune system suppression. In a normal pregnancy, the number of T cells may increase in order to enhance the fetal tolerance, but in patients with lupus, a decrease in the function of T cells has been observed, which can lead to poor prognosis in mothers with lupus (7-9).

Materials and Methods

For this mini-review, we used a variety of sources including PubMed, Embase, Scopus and directory of open access

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journals (DOAJ). The search was performed by using combinations of the following key words and or their equivalents; lupus nephritis, systemic lupus erythematosus, glomerular filtration rate, premature infants, anti- dsDNA antibody, Renal involvement, anti-phospholipid antibody, kidney disease, renal failure, proteinuria, poor fetal outcome and pregnancy.

Renal involvement

One of the most important causes of death in patients with lupus in the first decade is renal involvement. This defect is predominantly evidenced as lupus nephritis during pregnancy. The rate of active lupus nephritis in pregnancy is 4% to 30%, and in a person with a history of the previous recurrence of lupus nephritis is estimated to be 20% to 30% (10). However, there are rare reports of lupus nephritis as the first manifestation of disease in pregnancy (11). The active lupus nephritis is the biggest threat to the outcome of pregnancy in women with lupus. The range of abortion rates in patients with a history of SLE before pregnancy was 36-8% that reaches 52% in women who have active lupus nephritis during pregnancy. Most disease attacks in pregnant women were mild to moderate in severity, and severe attacks were only reported in 10% to 40% of patients. Most of the reported attacks involve blood, musculoskeletal and renal systems. In women with moderate to good disease control, the number of attacks is less. Disease-related attacks in mothers seem to be more related to the problems of premature infants. Studies have shown that active nephritis can be an independent factor in increasing fetal mortality. Disease activity six months before pregnancy is a prognostic factor for the development of lupus nephritis (12,13).

Physiologically, pregnancy increases glomerular filtration rate and increases blood volume, causing stress on the kidney system (1). These conditions in people with underlying kidney disease can cause further kidney damage (14). During normal pregnancy, glomerular filtration rate can increase by 50% and creatinine clearance by 30%. Creatinine levels ranged from 0.4 to 0.6 mg/dL is considered normal in a pregnancy and the value higher than 0.8 mg/dl is considered to be elevated.

Significant renal failure before pregnancy has been associated with poor fetal outcome and the likelihood of early delivery is higher in women whose proteinuria is in the nephrotic range. Serum creatinine higher than 140 mmol/L has been associated with a 50% chance of losing pregnancy and if the creatinine level exceeds 400 mmol/L, this probability increases up to 80%. Women with nephrotic syndrome are at increased risk for thrombosis and therefore, treatment with low doses of aspirin during pregnancy should be done regardless of the level of antiphospholipid antibodies.

Diagnostic laboratory tests

The level of anti-dsDNA antibody is associated with SLE (2). Women with a history of kidney disease, in addition to serially measuring serum creatinine, dsDNA and complementary levels (C3, C4) should be tested planned for 24-hour urine collection to measure creatinine clearance and proteinuria at least once a month. If proteinuria is detected in the urine analysis, urine samples should be sent for microscopic examination to detect glomerular red blood cells or RBC casts that are prognostic factors for active renal disease. A kidney biopsy should be conducted in any patient with lupus that has clinical or laboratory evidence of active nephritis (2). Immunosuppressive therapy in mothers with lupus is administered in two phases; as an induction therapy at the start of the diagnosis or during an attack phase and in the recovery phase as preservative treatment.

Treatment

The goal of lupus treatment is to normalize renal function or at least to prevent progression of renal dysfunction (15). Precise follow up of pregnant women with lupus, treatment of complications and also prevention of teratogenic side effects is important. Due to the teratogenicity of a wide range of immunosuppressive drugs including cyclophosphamide and mycophenolate mofetil, treatment for lupus nephritis is restricted. Selective treatment of the disease in pregnancy include corticosteroids and azathioprine are suitable modalities (16).

Patients with lupus nephritis, especially hypertensive patients and antiphospholipid syndrome, are susceptible to preeclampsia if they will be pregnant (17). The risk of preeclampsia in patients with lupus is between 10% and 35% and in women with creatinine levels above 2.8 mg/dL, the risk of preeclampsia and loss of pregnancy increases dramatically (18). In women with underlying kidney disease, the blood pressure should be controlled in a range lower than 140/90 mm Hg (19). The proposed drugs for pregnancy include methyldopa, nifedipine, diuretics, labetalol and hydralazine (20). Due to the possibility of embryonic anomalies, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs), should be avoided. Additionally, the administration of atenolol due to the possibility of an intrauterine growth retardation of the fetus should be avoided. Likewise, administration of spironolactone due to the anti-androgens property should be avoided (21). Additionally, in the case of anti-phospholipid antibody syndrome, anti-coagulants is necessary. Additionally in women with nephrotic range proteinuria, anti-coagulants should be prescribed due to increased coagulability. Aspirin should be prescribed to prevent preeclampsia. The administration of aspirin in mothers with lupus causes a better prognosis for fetus, for example it may reduce the incidence of abortion (22).

Good pregnancy prognosis can be predicted in pregnant women with lupus in the complete remission period. To achieve a successful pregnancy, pre-pregnancy counseling is required. The incidence of abortion, preterm labor and perinatal adverse events in people with lupus are higher than that of healthy women.

Conclusion

Thus, all pregnancies in patients with lupus should be considered as high risk and should be performed

in coordination with a gynecologist, perinatologist, rheumatologist and nephrologist. Several factors have been identified as the responsible for the loss of the fetus in lupus condition, but in the recent multivariate analysis, renal involvement has been revealed as the most important predictor. Anti-phospholipid antibodies (APA) test positivity can indicate the increased risk for poor prognosis. It seems that complete control of the patient's condition before fertilization such as being in complete remission at the beginning of pregnancy, lack of hypertension or renal failure, APA negativity and use of anticoagulant drugs can greatly improve the outcome of pregnancy.

Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. SB and MA searched and gathered the papers. MB prepared the primary draft. KM edited the manuscript and conducted the final revision and all authors read, revised, and approved the final manuscript.

Conflicts of interest

There were no points of conflicts to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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