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Ovarian Function and Reproductive Outcomes of the Female Patients with Systemic Lupus Erythematosus and the Strategies to Preserve their Fertility

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Abstract

Systemic lupus erythematosus (SLE) is a chronic auto-immune systemic disease that mainly affects women at reproductive age. Unfortunately, reproductive function of the young female patients suffering from this disease is commonly compromised by different etiologies. First, ovarian reserve is diminished even in the presence of mild disease suggesting a direct impact of the disease itself on ovarian function possibly due to ovarian involvement in the form of autoimmune oophoritis. Second, SLE patients with severe manifestations of the disease are treated with alkylating chemotherapy agent cyclophosphamide. Cyclophosphamide and other drugs of alkylating category have the highest gonadotoxicity. Therefore SLE patients exposed to cyclophosphamide have a much higher risk of developing infertility and premature ovarian failure than do the counterparts who are treated with other less toxic treatments. Third, the functions of the hypothalamic pituitary ovarian axis are pertubed by chronic inflammatory state. And finally adverse pregnancy outcomes are more commonly observed in SLE patients such as fetal loss, preterm birth, intrauterine fetal growth restriction, preeclampsia-eclampsia and fetal congenital heart blocks. We aimed in this review article to provide an update on the ovarian function and other reproductive outcomes in SLE patients, and the current strategies to preserve their fertility in the lights of the most recent guidelines of fertility preservation.

Keywords: Fertility preservation; Systemic lupus erythematosus; Chemotherapy; Ovary

Introduction

Systemic lupus erythematosus is a systemic chronic inflammatory disease of autoimmune origin [1]. It has a predominant female predilection (9:1) and manifests itself during reproductive years. Women, especially in their 20s and 30s, are affected more frequently than men. Patients with SLE are subject to myriad symptoms, complaints, and inflammatory involvement that can affect virtually every organ [2]. The increased frequency of SLE among women has been attributed in part to the effects of estrogen hormone [3]. A number of observational studies suggested an estrogen effect including the female-to-male ratio of SLE in different age groups. For instance, in children, in whom sex hormonal effects are presumably minimal, the female-to-male ratio is 3:1. But in adults especially in women of child-bearing years, the ratio ranges from 7:1 to 15:1. In postmenopausal women the ratio is approximately 8:1 [4], the Nurse's Health study provided another evidence supporting the potential role of estrogens in predisposing to SLE by showing that women with early menarche, or treated with estrogen-containing regimens such as oral contraceptives or postmenopausal hormone replacement therapies, have a significantly increased risk for SLE (hazard ratios of 1.5 to 2.1) [5,6]. Interestingly, apart from estrogen hormone itself factors related to the X chromosome may also be important in predisposing women to SLE. At least three predisposing gene variants located on X chromosomes have been identified (IRAK1, MECP2, TLR7) [7]. There is also evidence for a gene dose effect, since the prevalence of XXY (Klinefelter's syndrome) is increased 14-fold in men with SLE when compared with the general population of men, whereas XO (Turner's syndrome) is underrepresented in women [8]. Other possibilities should be taken into account that can explain female predilection of this disease include X-inactivation, X chromosome demethylation, imprinting, X or Y chromosome genetic modulators, differential methylation of DNA and acetylation of histones bound to DNA, intrauterine influences, chronobiologic differences, pregnancy, and menstruation [9,10].

As a striking example of altered immunologic and hormonal environments pregnancy itself can cause an exacerbation or can even trigger the first symptoms of lupus; a relapse is more likely to develop in the immediate postpartum period (puerperium) [11]. The hormonal adjuvants used for ovulation induction and in vitro fertilization may cause exacerbations of SLE [12] providing further evidence for the role of hormones in SLE. Sex steroid hormones, namely estradiol, testosterone, progesterone, dehydroepiandrosterone (DHEA), and pituitary hormones, including prolactin, have immunoregulatory roles; therefore can modulate the incidence and severity of SLE [1,5,13]. The use of estrogen-containing contraceptive agents is associated with a 50 percent increase in risk of developing SLE; while either early onset of menarche (age ≤ 10 years) or administration of estrogen to postmenopausal women doubles their risk [14]. In this review article we aimed to provide an update on the impact of systemic lupus erythematosus and therapies on reproductive function and current fertility preservation strategies in women suffering from this disease.

Adverse Reproductive Outcomes in Women with Systemic Lupus Erythematosus

Reproductive function of women with SLE can be compromised by different mechanisms as follows;

- Chronic inflammatory state may prevent the proper functioning of the hypothalamic-pituitary-ovarian axis (HPO) [15]
- Autoimmune ovarian injury most commonly in the form of autoimmune oophoritis may hamper ovarian function [16]
- Lupus flares are associated with hyperprolactinemia, which may interfere with ovulation process and affect immune activity [17]
- Thrombocytopenia, antiphospholipid antibodies, and the use of glucocorticoids and/or nonsteroidal anti-inflammatory drugs can contribute to menorrhagia [14]
- Temporary or even permanent early (or premature) amenorrhea may result from autoimmune ovarian injury or from the administration of cytotoxic agents such as cyclophosphamide [18]

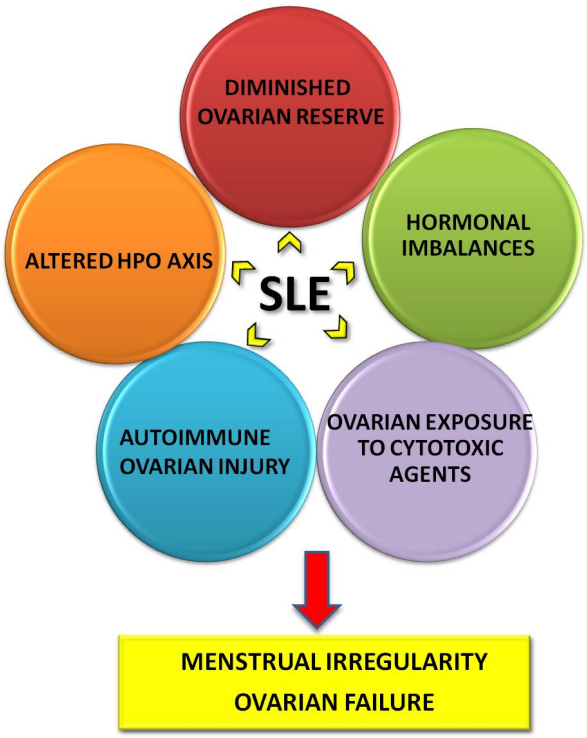

Figure 1: Contributory factors causing menstrual irregularity, ovarian failure and infertility in women with systemic lupus erythematosus. SLE involves many organ systems. The ovarian function can be compromised both autoimmune oophorotis; and by gonadotoxic effects of cyclophosphamide. In addition, hormonal imbalances and altered hypothalamic pituitary ovarian axis can further contribute to ovarian dysfunction culminating in menstrual irregularity, infertility and ovarian failure.

The clinical manifestations of these abnormalities are menstrual irregularity, absence of menses (amenorrhea) or premature ovarian failure (Figure 1). Menstrual irregularities are frequently observed in patients with SLE and many of them are associated with the activity of the disease [19]. Indeed, SLE itself induces dysfunction in the HPO axis, elevates serum prolactin and lowers progesterone levels along with higher follicle stimulating hormone (FSH) and lower luteinizing hormone (LH) levels. For instance one study showed in juvenile SLE patients that menstrual abnormalities and longer length cyclophosphamide were more frequently observed in JSLE than controls (63% vs. 10%, P=0.0001; 23% vs. 0%, P=0.0105, respectively). The median of follicle stimulating hormone was significantly higher in patients with JSLE compared with controls (4.6 vs. 3.4 IU/L, P=0.0207), and the median of progesterone was lower (32.5 vs. 70 ng/mL, P=0.0033). The median of luteinizing hormone was lower in patients with JSLE with menstrual abnormalities versus normal cyclophosphamide (2.9 vs. 5.5 IU/L, P=0.019) and both had a high percentage of decreased progesterone levels (63% vs. 73%, P=0.70) regardless of the use of IV cytotoxic therapy [15]. Obviously elevated FSH levels in these patients shows decreased ovarian reserve and/or response to gonadotropins. Other studies also obtained similar findings by documenting reduced estradiol, and higher FSH, LH and prolactin levels in SLE patients compared to healthy age-matched controls [19].

In support of these findings, a recent study compared the levels of anti-mullerian hormone as a hormonal marker of ovarian reserve between SLE patients and healthy controls and found that SLE patients had significantly lower AMH levels than the controls. More interestingly, they did not find any correlation between the activity of the disease as measured using SLEDA1 and ECLAM and AMH values [20]. These important findings clearly illustrates that SLE itself has a negative influence on ovarian reserve and function regardless of the activity of the disease and exposure to cytotoxic immunosuppressive therapies.

The Impact of Cytotoxic Immunosuppressive Therapies on Ovarian Function and the Predictors of Ovarian Failure in Women with SLE

Moderate and severe lupus nephritis, alveolar hemorrhage, vasculitis and CNS involvement are the indications for the use of immunosuppressive agents such as mycophenolate, azathioprine, or cyclophosphamide. Among these drugs, cyclophosphamide has the most devastating effects on the ovary. In order to make it clearer and easily understandable to the readers in the fields outside the reproductive medicine, we first will provide some fundamental information about normal ovarian physiology in women.

An adult human ovary harbors two different types of follicles; dormant (quiescent) primordials and the growing follicle fractions. Follicles are the functional apparatus of the ovary and consist of an oocyte surrounded by granulosa and theca cells of somatic origin.

Primordial follicles represent the earliest stage of follicular development. Ovarian reserve is determined by the number of quiescent primordial follicles in the ovary. Dormant primordial follicles constitute >90% of the follicle pool in the human ovary with only a small fraction belonging to the growing follicle pool at the primary stage and beyond [21]. Primordial follicles do not express FSH receptor; their growth is not under the control of gonadotropins [22]; do not produce inhibins or anti-mullerian hormone (AMH) and are not visible on ultrasound [23]. While there is no direct marker of primordial follicle number, ovarian reserve can be estimated by evaluating the hormonally active and visible growing follicle pool using anti-mullerian hormone (AMH), antral follicle counts (AFC) and early follicular FSH levels. Any toxic insult that preferentially

targets primordial follicles such as alkylating agents leads to a decrease in reproductive life span and possibly premature ovarian failure. If the loss of ovarian function develops during or shortly after the completion of therapy, it is termed acute ovarian failure (AOF). For those who retain ovarian function after the completion of gonadotoxic chemotherapy a subset will go on to experience menopause prematurely before age 40 [24]. Chemotherapy agents, particularly those of alkylating category such as cyclophosphamidelophosphamide have the highest gonadotoxic potential. The index drug cyclophosphamidelophosphamide is metabolized to two active metabolites in the body, phosphoramide mustard and acrolein. While acrolein exerts its toxicity on the bladder causing hemorrhagic cystitis, phosphoramide mustard is the main product that is responsible for the follicular damage in the ovary [25]. It causes ovarian damage by inducing apoptotic death of the oocytes and somatic granulosa cells (Figure 2). The clinical manifestations of ovarian damage in women at reproductive age vary from temporary menstrual irregularity to amenorrhea, infertility and premature ovarian failure depending upon the magnitude of the damage. The probability of developing permanent ovarian failure depends on the following factors: patient's age, and the type, dose and duration of the treatment. If the patient is older and her ovarian reserve is low, they are less likely to retain or regain menstrual function than younger ones. It should be remembered that menstrual status may not be a reliable indicator of the extent of the impact of chemotherapy since many patients may experience transient menstrual irregularities and amenorrhea during chemotherapy [26]. A portion of these patients resumed menses in the following months depending upon the age of the patients, and the type and the dose of chemotherapy regimens administered. Patients younger than age 40 are more likely to retain or regain menstrual function than those older than age 40 (22-56% vs. 11%) [26]. Furthermore patients with critically diminished ovarian reserve and elevated FSH values may continue to menstruate [27]. Therefore menstrual function is a crude indicator of ovarian reserve. To monitor the changes in ovarian reserve during and after chemotherapy administration non-invasive hormonal markers of ovarian reserve can be a good alternative. FSH, Anti-mullerian hormone (AMH), antral follicle count (AFC) have been utilized for this purpose. Measurement of basal FSH levels on cyclophosphamide day 2 or 3 is one of the most widely used screening tests for the assessment of ovarian reserve. It has been well-established that higher FSH levels (>10 mIU/mL) during early follicular phase are an indicator of decreased ovarian reserve and lower success rates in assisted reproduction. Although no direct correlation has been documented between the number of primordial follicles in the ovary and FSH levels, the basal FSH level will rise as the number of follicles decline in the ovary due to the regulation of FSH secretion at hypothalamus and pituitary through a feedback control of inhibin B and estradiol. Anti-mullerian hormone (AMH), a member of transforming growth factor beta family like inhibins produced by the granulosa cells of growing preantral and small antral follicles has emerged as a reliable marker of ovarian reserve [28]. Serum AMH levels correlate well with the number of antral follicles in the ovary [29] and the number of oocytes retrieved in IVF cyclophosphamide [30]. AMH was more consistently correlated with the clinical degree of follicle pool depletion in young women presenting with elevated FSH levels [31]. Currently serum AMH levels and the number of antral follicles counted on the ultrasound at early follicular phase of the menstrual cycle are the most reliable indicators of ovarian reserve.

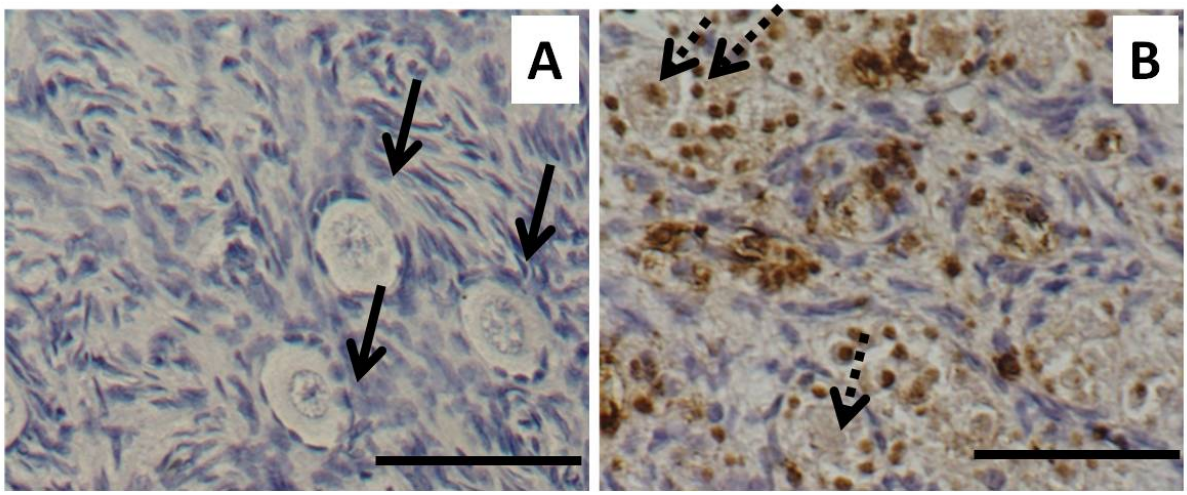

Figure 2: An adult human ovary with dormant primordial follicles before and after exposure to cyclophosphamide. The number of quiescent primordial follicles determines ovarian reserve. Solid arrows in the figure A show healthy primordial follicles whereas dashed arrows in the figure B point apoptotic death of the oocytes and surrounding granulosa cells after exposure to cyclophosphamide. Scale bars 100 microns.

In the recent years a number of studies documented that cyclophosphamide administration is the most significant risk factor for ovarian failure, and that AMH is a sensitive and reliable marker of ovarian reserve and damage post exposure to cyclophosphamide in female patients with SLE [18-20,32-34]. For instance, Harward et al. reported a case series study of women diagnosed with SLE, vasculitis and scleroderma prior to age 35 (23 had prior cyclophosphamide exposure, 20 did not). In their series, even though women with prior cyclophosphamide exposure were 4 years younger at diganosis than those without cyclophosphamide, 30.4% of them had cessation of menses compared to 0% of those without cyclophosphamide ($p<0.05$). Of the women with prior cyclophosphamide exposure those with loss of menses were older at study enrollment, older at cyclophosphamide treatment and higher cumulative doses of cyclophosphamide than those who retained menstrual function [18].

AMH appear to be a reliable indicator of residual ovarian reserve postexposure to cyclophosphamide based on the accumulating evidence of the aforementioned studies. But the role of this hormone in predicting the probability of subsequent pregnancy is questionable. A very recent matched cohort study consisting of 56 cyclophosphamide exposed and 56 non-exposed SLE patients found that the risk of failure to conceive was associated with cumulative cyclophosphamide dose (p=0.007) and older age (p=0.02), but not with AMH levels [35].

As emphasized in the previous section, older patient and higher dose of cyclophosphamide are associated with the higher risk of menstrual dysfunction and ovarian failure. As a striking example, one study compared two different doses of cyclophosphamide (75 vs. 50 mg/body surface) in SLE patients receiving pulse cyclophosphamide therapy. More patients treated with 75 mg/m^2 cyclophosphamide had sustained amenorrhea (17.5% vs. 0%, p<0.05) independently associated with treatment duration (p=0.001) and total IV cyclophosphamide dose (p=0.02) [33]. The results of LUMINA LVIII, a multiethnic US cohort study showed that disease activity and Texan-Hispanic ethnicity and cyclophosphamide induction therapy emerged as predictors of ovarian failure in addition to well documented association of the risk of gonadal failure with the use of cyclophosphamide and older age [36].

Other immunosuppressive agents are less detrimental to the ovaries than cyclophosphamide

Several clinical studies and meta-analyses compared cyclophosphamide with other immunosuppresive agents in terms of disease remission and side effects such as amenorrhea and ovarian failure. One of them compared ovarian toxicity of cyclophosphamide with mycophenolate mofetil, azathioprine and calcineurin inhibitors using serum AMH levels in 216 patients (mean ± SD age 35.1± 10.1 years, mean ± SD SLE duration 7.6 ± 5.9 years). The mean ± SD AMH level was significantly lower in patients previously exposed to cyclophosphamide therapy than in those who had not been exposed after adjustment for age (1.58 ± 2.92 versus 1.73 ± 2.11 ng/ml; P=0.04). The median time interval between the AMH assay and the last dose of cyclophosphamide administered was 6.7 years (interquartile range 3.4–8.5). AMH levels in users versus nonusers of other immunosuppressive agents, including mycophenolate mofetil (MMF), azathioprine, and the calcineurin inhibitors, were not statistically different. Linear regression revealed increasing age (beta -0.32, P=0.02) and each 5 gm of cyclophosphamide exposure (beta -0.28, P= 0.047) were independently associated with a lower AMH level [32]. The results of a meta-analysis of seven clinical trials in 725 SLE patients found that lower risks of leukopenia, amenorrhoea and alopecia, and a higher risk of diarrhea were found with mycophenolate mofetil compared to cyclophosphamide [37]. Other two meta-analyses obtained similar findings by showing that significantly fewer patients receiving MMF developed amenorrheea [11,38].

The Outcomes of Pregnancy in Patients with Systemic Lupus Erythematosus

SLE is more common in women of childbearing age. Even though patients with SLE are as fertile as women in the general population, their pregnancies may be associated with complications. Clinical or subclinical inflammation, presence of autoantibodies, hormonal dysfunction, and immune alterations of lupus contribute to pregnancy complications. Impairment of early placental development leads to poor vascularization, resulting in placental ischemia and subsequent endothelial damage. Depending on the extent of the pathological process, pregnancy loss, IUGR, and preeclampsia can develop (Figure 3) [12].

The prognosis for both mother and child is best when SLE has been quiescent and when renal disease in remission for at least six months prior to the pregnancy [39]. A pregnant patient with SLE should be considered as a high risk pregnancy if one or more of the following features are present [40]:

- Prior history of poor obstetric outcomes
- Renal involvement
- Cardiac involvement
- Pulmonary hypertension
- Interstitial lung disease
- Evidence of active lupus
- High-dose glucocorticoid therapy
- Immunosuppressive therapy
- Antiphospholipid antibodies/syndrome
- Antibodies to Ro/La (predisposing to neonatal lupus)
- Multiple gestation

The extent of the cardiac, pulmonary and renal complications of the disease during pregnancy should be investigated thoroughly as they are associated with a considerable risk for the health of mother and fetus. For instance, the findings of LUMINA (LVI) study showed us that adverse outcomes occurred in 63.7% of 102 pregnancies. Texan Hispanic and African American ethnicities, fewer years of education, higher number of ACR criteria, renal involvement, glucocorticoid exposure and the maximum dose of glucocorticoids used prior to the pregnancy outcome were associated with an adverse pregnancy outcome [41]. The presence of any of the following characteristics during pregnancy should alert obstetrician for the risk of serious adverse outcomes [40].

- Severe pulmonary hypertension (mean pressure >50 mmHg)
- Restrictive lung disease (forced vital capacity <1 liter)
- Heart failure
- Chronic renal failure (creatinine >2.8 mg/dL)
- Active renal disease
- History of severe preeclampsia or HELLP syndrome
- Stroke within the previous six months
- Severe lupus flare within the previous six months

Therefore, after a carefull discussion with the patient, a decision to pursue pregnancy should be carefully considered and made with an awareness of the potentially serious consequences. Patient should be informed that systemic lupus erythematosus may exacerbate during pregnacy and that adverse pregnancy outcomes such as fetal loss, intrauterine growth retardation, preterm labor and delivery and preeclampsia occur more frequently in pregnant women with SLE [42].

Lupus nephritis in pregnancy

Lupus nephritis is particularly important during pregnancy from different aspects. First, as a general rule patients with organ damage at the time of pregnancy may have difficulty since pregnancy imposes an added burden on malfunctioning organs. This phenomenon is

especially important in patients with renal disease. Second, pregnancy in women with lupus nephritis is associated with an increased risk of fetal loss (up to 75 percent) and with worsening of the renal and extrarenal manifestations as documented by many studies [43,44]. Third, patients with preexisting hypertension, proteinuria, and azotemia are at increased risk for renal exacerbations and pre-eclampsia during pregnancy [45]. Since severe renal exacerbations can occur during pregnancy women with lupus nephritis should be encouraged to delay pregnancy until the disease can be rendered inactive for at least six months [44]. While avoiding or minimizing the use of glucocorticoids and immunusuppressive drugs at conception and during pregnancy may help reduce the risk of adverse effects upon the fetus, it may be preferable in some patients to continue glucocorticoids at the lowest effective dose and/or to cautiously use azathioprine.

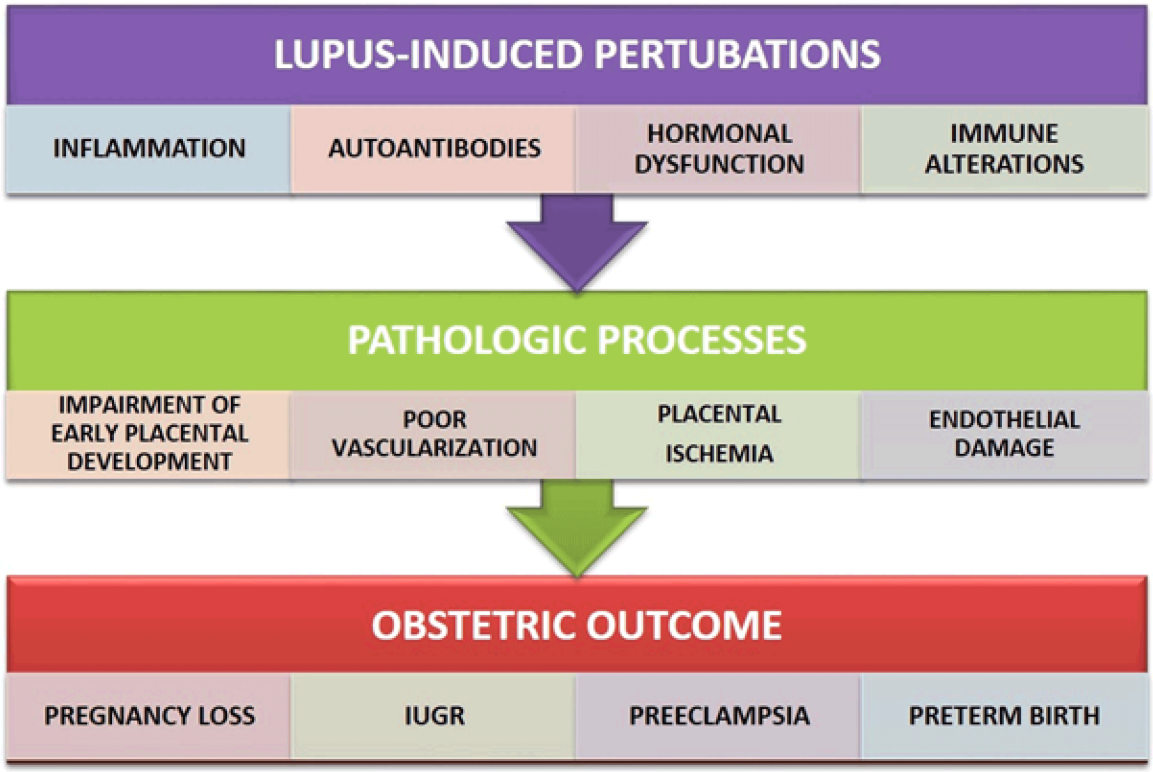

Figure 3: Adverse obstetric outcomes in patients with SLE. Systemic abnormalities induced by lupus cause a series of pathological processes leading to poor obstetric outcomes in women.

For instance, LUMINA (LVI) study showed us that renal involvement was independently associated with an adverse pregnancy outcome [Odds ratio (OR)=5.219 (95% (CI) 1.416-19.239, p=0.0131] as were the maximum dose of glucocorticoids used prior to the pregnancy outcome (OR=1.028; CI: 1.002-1.054; p=0.0315) and fewer years of education (OR=1.204; CI: 1.006-1.472; p=0.0437) [41]. Other studies showed adverse effects [42]. Indeed, a very recent study showed that renal flares and adverse pregnancy outcomes were lowered in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. 54 women [23 treated with MMF (group 1) and 31 treated with AZA (group 2)] were included in this study. MMF dosage was tapered and subsequently transferred to AZA, which was maintained throughout pregnancy. Three (13%) patients (group 1) vs. none (group 2) developed a renal flare 3-6 months after transitioning from MMF to AZA (P=0.14) before pregnancy ensued. The only parameter with a significant difference in those with flare compared with those without was younger age (median 27 vs. 30 years; P=0.03). Risk for adverse outcome within 48 pregnancies (pre-eclampsia 9%, preterm delivery 20.5%) increased with every milligram of prednisone dosage [odds ratio (OR) 2.03] and every single unit of SLEDAI score (OR 3.92). Renal flares occurred post-partum in two women. No patient developed worsening of renal function [46].

Preeclampsia

Preeclampsia is a frequent complication of pregnancy in SLE, occurring in approximately 13 percent of patients [47]. If the patient has renal disease, the incidence may be much higher up to 66 % [48]. Since their clinical presentations are similar, it is often difficult to distinguish preeclampsia from lupus nephritis or a lupus flare. Furthermore, preeclampsia is more likely to occur in patients with antiphospholipid antibodies (aPL), diabetes mellitus, or a prior episode of preeclampsia. Preexisting thrombocytopenia may also be a risk factor [49]. The following laboratory guidelines may be useful in differentiating preeclampsia from nephritis or a lupus flare in pregnant patients:

While urinanalysis reveals only proteinuria in preeclampsia, lupus nephritis is often associated with proteinuria and/or active urine sediment (red and white cells and cellular casts);

Hypocomplementemia and increased titers of anti-DNA antibodies are hallmarks of flares of SLE, but complement levels are usually but not always normal or increased in preeclampsia [50,51];

Thrombocytopenia, elevated serum levels of liver enzymes and uric acid, and decreased urinary excretion of calcium are more prominent in preeclampsia than lupus nephritis. However, thrombocytopenia may also be seen in association with aPL, thrombotic thrombocytopenic purpura, and immune thrombocytopenia, each of which may complicate pregnancy in women with SLE.

Fetal loss and intrauterine growth retardation

Intrauterine death of the fetus and fetal growth restriction are other common adverse outcomes of pregnances complicated by SLE. Active lupus, lupus nephritis, prexisting hypertension, hypocomplementemia, elevated levels of anti-DNA antibodies, antiphospholipid antibodies and thrombocytopenia are particularly associated with the higher risk for fetal loss up to 50 percent [52,53]. Anti-DNA antibodies may potentiate pregnancy loss by cross reacting with laminin, a molecule critical for placenta implantation [54]. In a meta-analysis by Smyth et al. [55] thirty-seven studies with 1842 patients and 2751 pregnancies were included. Maternal complications included lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), pre-eclampsia (7.6%), and eclampsia (0.8%). The induced abortion rate was 5.9%, and when excluded, fetal complications included spontaneous abortion (16.0%), stillbirth (3.6%), neonatal deaths (2.5%), and intrauterine growth retardation (12.7%). The unsuccessful pregnancy rate was 23.4%, and the premature birth rate was 39.4%. Meta-regression analysis showed statistically significant positive associations between premature birth rate and active nephritis and increased hypertension rates in subjects with active nephritis or a history of nephritis. History of nephritis was also associated with pre-eclampsia. Anti-phospholipid antibodies were associated with hypertension, premature birth, and an increased rate of induced abortion. And very recently PORTO study (The Prospective Observational Trial to Optimize Paediatric Health in IUGR (PORTO) Study) recruited 1,200 ultrasound-dated singleton IUGR pregnancies, defined as EFW <10th centile, between 24+0 and 36+6 weeks gestation. Perinatal deaths occurred between 24+6 and 35+0 weeks gestation corresponding to birthweights ranging from 460 to 2260 grams. Perinatal deaths occurred more commonly in pregnancies with severe growth restriction (EFW<3rd centile) and associated abnormal Doppler findings resulting in earlier gestational ages at delivery and lower birthweights. All of the described pregnancies were complicated by either significant maternal comorbidities, e.g. hypertension, systemic lupus erythematosus (SLE) or diabetes, or poor obstetric histories, e.g. prior perinatal death, mid-trimester or recurrent pregnancy loss. All perinatal deaths showed abnormalities on placental histopathological evaluation [56].

Neonatal lupus

Neonatal lupus is a passively transferred autoimmune disease as a result of placental transfer of maternal anti-Ro/SSA and/or anti-La/SSB antibodies to the fetus. The most serious complication in the neonate is complete heart block, which occurs in approximately 2 percent of such pregnancies. Isolated skin rash occurs in a similar percentage. Maternal use of hydroxychloroquine (HCQ) may be associated with reduced rates of the cardiac manifestations in the newborn, including congenital heart block and isolated cardiomyopathy, and maternal HCQ use is also associated with a decreased risk of recurrence of cardiac neonatal lupus in subsequent pregnancies [57,58].

The Options to Preserve Fertility in Young Women with Lupus

The same guidelines of fertility preservation used in female cancer patients who are at the risk of ovarian damage, infertility and premature menopause as a result of exposure to cytotoxic chemotherapy regimens should be adopted for young women with SLE who will receive cytotoxic immunosuppresive therapies and have concerns about their future fertility. These patients should be counseled with a reproductive endocrinologist who has an expertise in fertility preservation strategies prior to receiving such gonadotoxic therapies. At initial consultation the patients first should be discussed about the risks of ovarian failure and other adverse reproductive and pregnancy outcomes related to the disease activity of lupus and postexposure to cytotoxic therapies. And then the available options of fertility preservations should be discussed with the patient and the most suitable one should be offered in the lights of the most recent guidelines and recommendations of fertility preservation. It is of crucial importance to inform the patient that female patients with SLE are prone to several poor obstetric outcomes if they become pregnant, and may have diminished ovarian reserve due to the impact of SLE on ovarian function regardless of the exposure to cytotoxic therapies.

Currently three main fertility preservation strategies are available in the females who are at risk of ovarian damage and failure as a consequence of exposure to gonadotoxic chemotherapy regimens. As stressed in the clinical guidelines by the American Society of Clinical Oncology and the practice committee opinion of the International Society for Fertility Preservation [59,60], all patients who will receive cytotoxic therapies for cancer and other non-malignant diseases and who are with interest in future fertility should be referred for consideration of fertility preservation. Currently embryo and oocyte freezing are the established fertility preservation methods according to the most recent guidelines of American Society for Reproductive Medicine, and Society for Assisted Reproductive Technology [61]. Other options include ovarian tissue cryopreservation, the use of gonadotropin releasing hormone agonist concurrent with chemotherapy administration, and *in vitro* maturation (IVM).

Embryo freezing

Embryo cryopreservation is the most established fertility preservation technique for patients with partners and sufficient amount of time before cancer treatment. According to the data from the Society for Assisted Reproductive Technology and the European IVF Monitoring Program clinical pregnancy rate per frozen-thawed embryo exceeds 30% in women younger than 35 years [62]. Conventional ovarian stimulation protocols are characterized by multi-follicular development in the ovary, and a much higher (10-20 times) blood levels of endogenously produced estrogens than natural cycle. Estrogen hormones play roles in immunity. Under normal conditions they enhance the humoral B cell immune response in humans, and at the same time seem to play important roles in pathophysiology of autoimmune rheumatic diseases [63]. In fact, evidences from clinical studies documented that menstrual cycle, pregnancy, and menopausal status that are characterized by fluctuations of endogenous estrogens significantly influence the course of autoimmune diseases [64]. Therefore it should be kept in mind that ovarian stimulation and rising estrogen hormone levels in lupus

patients may trigger the flares of the disease [65]. This is particulary important in SLE patients with cardiac valvulopathy and/or antiphospholipid antibodies, which increase the tendency for thrombosis. This risk is further aggrevated in the case of ovarian hyperstimulation syndrome, characterized by supraphysiological estrogen levels, multifollicular development, ascites, pelural effusion, increased vascular permeability, intravascular constriction with an increased risk for thrombo-embolism [66]. In order to minimize the risk of disease flare, thrombosis and other complications, mild ovarian stimulation with low dose gonadotropins, avoidance of ovarian hyperstimulation and the prophylactic use of anticoagulants should be considered in these patients.

Oocyte freezing

Oocyte cryopreservation is ideal for women who do not have a partner and do not want to use donor sperm for fertility preservation. It does not require fertilization after egg retrieval, thus creation of unnecessary embryos can be prevented. However, since ovarian stimulation is required before egg retrieval, the same recommendations in the embryo freezing also applies to oocyte freezing to prevent disease flare and other complications.

Oocyte cryopreservation has been considered as an experimental procedure until 2012. Previously, most oocytes were cryopreserved by slow freezing, and pregnancy rates with cryopreserved oocytes were significantly low to be considered as an established assisted reproduction technology (ART). However, significant advances in cryopreservation methods with wide use of vitrification since 2006 have changed the course and status of oocyte cryopreservation in ART. With the dramatic increase in success with vitrification during recent years, the rates of ongoing pregnancy, top-quality embryo, embryo cleavage, and fertilization do not differ between the vitrified and the fresh oocyte groups [67]. When the data from 1998-2008 is analyzed, oocyte survival rate was higher in vitrified group (81%) compared to the slow freezing group (68%). The live birth rate per embryo transfer (after fertilizing the thawed/warmed oocytes) was 14% and 34% in the slow frozen and vitrified group, respectively [68]. Cobo et al. reported that clinical pregnancy rates of IVF cycles with vitrified oocytes did not differ from those of fresh IVF cycles (55.4% vs. 55.6% per transfer) [69]. Nevertheless, the live birth rates per fresh mature oocyte and per vitrified oocyte have been low (4-6% vs. 4.5%) according to the results of several meta-analyses [69-71]. Moreover, the number of oocytes harvested and the live birth rate per oocyte further decrease with chronologic aging, especially after the age of 37. For instance, the live birth rate per mature oocyte is 4.47% for women under 37. From the age of 38 and onwards, a significantly lower rate is noted, declining from 3.80% at the age of 38 to 0.78% at 43 [70]. At this point one may ask "how many oocytes should be frozen to achieve a live birth?" A recent longitudinal cohort multicentric study has provided an answer to this question by showing that more than eight oocytes are required to improve live birth rates (22.6 versus 46.4%). When fewer oocytes are available in women aged >38 years, results are dramatically reduced (12.6 versus 27.5%) [72]. These figures are extremely useful in order to provide accurate information on the realistic success rate of oocyte freezing when counseling breast cancer patients who wish to have their oocytes frozen for the successful pregnancy in the future. Another important issue about gamete freezing is the risk of congenital anomalies in the offspring. To date, no apparent increase in the rate of congenital anomalies has been reported as compared to US national statistics for natural conceptions reported by the CDC [68]. As there is clear evidence that overall success rates of oocyte cryopreservation are comparable to those of embryo cryopreservation, the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology finally announced that oocyte cryopreservation should no longer be considered experimental [61]. The fact that the ASRM removed the "experimental" label from oocyte cryopreservation will facilitate broader use of oocyte cryopreservation and reinforce the value of this strategy for fertility preservation in patients seeking to preserve their fertility.

Ovarian tissue freezing

Ovarian tissue cryopreservation is the only option of fertility preservation in cancer patients in whom cancer therapy cannot be delayed because of a rapidly growing tumor; or ovarian stimulation is contraindicated for embryo or oocyte freezing. Ovarian tissue cryopreservation does not require ovarian stimulation and ovarian tissue can be harvested laparoscopically without any preparation. Removed tissue is processed into thin cortical slices and frozen via slow freezing. This procedure is much less successful than embryo and oocyte cryopreservation in terms of live birth rate. Ovarian tissue cryopreservation has become a clinically feasible technology for fertility preservation in cancer patients since Donnez [73] reported the first live birth after orthotopic autotransplantation of frozen-thawed human ovarian tissue in 2004. To date, this strategy is the only fertility preservation option for pre-pubertal girls who will receive cytotoxic chemotherapy regimens. Therefore any pre-pubertal and adolescent girls who are required to receive immediate cyclophosphamide therapy for fulminant SLE can be considered for ovarian tissue freezing. According to the data of fertiPROTEK network, 16 patients with SLE had their ovaries frozen prior to cytotoxic chemotherapy regimens [74].

Gonadotropin releasing hormone (GnRH) analogues for the protection against cytotoxic therapy induced ovarian damage

GnRH analogues suppress ovarian function by inhibiting the secretion of FSH and LH from anterior pituitary gland, thus creating a hypoestrogenic hypogonadotropic environment.

After the promising results of some anectodal reports of case series showing a beneficial effect of GnRH administration against chemotherapy induced amenorrhea in cancer patient, several randomized controlled trials were conducted in cancer patients to assess the role of GnRH in the prevention of ovarian failure induced by chemotherapy. Unfortunately the results of these studies are conflicting. Some demonstrated a protective effect of the drug while the others did not. For instance, the PROMISE-GIM6 study (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6), a parallel, randomized, open-label, phase 3 superiority trial enrolled 281 premenopausal women with stage I through III breast cancer randomly assigned to receive chemotherapy alone or chemotherapy plus triptorelin. Twelve months after the last cycle of chemotherapy, the rate of early menopause was 25.9% in the chemotherapy-alone group and 8.9% in the chemotherapy plus triptorelin group, an absolute difference of -17% (95% confidence interval, -26% to -7.9%; P<0.001). The odds ratio for treatment-related early menopause was 0.28 (95% confidence interval, 0.14 to 0.59; P<0.001) [75]. By contrast the GBG 37 ZORO study failed to show any protective effect of GnRH analogue against chemotherapy induced ovarian failure in breast cancer patients. The study included 60 patients younger than age 46 years with hormone-insensitive breast cancer randomly allocated to

receive AC+T neoadjuvant chemotherapy with or without GnRH analogue goserelin administered at least 2 weeks before the first chemotherapy cycle, continuing at 3.6 mg subcutaneously every 4 weeks until the end of the last cycle. Fifty-three patients (88.3%) experienced temporary amenorrhea (93.3% with vs. 83.3% without goserelin). No significant difference was observed regarding the reappearance of menstruation at 6 months after chemotherapy (70.0% with v 56.7% without goserelin; difference of 13.3%; 95% CI, -10.85 to 37.45; P=0.284). Time to restoration of menstruation was 6.8 months (95% CI, 5.2 to 8.4) with goserelin and 6.1 months (95% CI, 5.3 to 6.8) without goserelin (P=0.304) [76].

Similar to the findings of the ZORO trial two recent randomized studies could not show any protective effect of GnRH analogues against postchemotherapy ovarian failure in breast cancer patients [77,78]. Finally one last meta-analysis of five randomized controlled trials of GnRH agonists administered concurrently with chemotherapy to prevent chemotherapy-induced ovarian toxicity in premenopausal women with breast cancer showed that significantly fewer women treated with GnRH agonist experienced post-chemotherapy ovarian failure, yielding a RR of 0.40 (vs. chemotherapy alone, 95% confidence interval [CI] 0.21-0.75). In contrast, both treatment groups experienced similar rates of resumed menses and spontaneous pregnancy [79].

Unfortunately, there is no randomized clinical trial launched so far to assess the protective effects of GnRH agonist on ovarian function in women with SLE exposed to cytotoxic chemotherapy. But, even though the emerging data from cancer patients is inconclusive, it appears from fertiPROTEKT network data that a great majority of SLE patients opted to receive GnRH analogues before cytotoxic therapies. According to that data a total of 2836 patients were advised prior to cytotoxic treatment in one of the FertiPROTEKT centres during January 2007 to November 2011. Of those, 68 patients (mean age 25 ± 6.07 years) were counseled for severe SLE. Only five women did not make use of a fertility preservation method. Sixty-three patients (92.6%) decided in favor of a fertility preservation method. The largest proportion (91.2%) opted for treatment with a GnRH analogue. Ovarian tissue removal for cryoconservation was performed in 16 patients (25%). Stimulation therapy for cryoconservation of fertilized egg cells was performed in three patients (4.4%) [74]. We strongly suggest that any SLE patient who opted to receive GnRH analogues before cytotoxic therapy should be informed that GnRH may not protect their ovaries against chemotherapy induced damage and therefore, an additional established backup method of fertility preservation such as embryo or oocyte freezing should be considered before starting chemotherapy.

Psychological Aspects of Having A Chronic Debilitating Disease and Compromised Fertility in Women with SLE

As in the other chronic diseases, psychological problems related to reductions in health related quality of life (HRQOL) are observed in SLE patients. Common SLE symptoms known to contribute to poor HRQoL include fatigue, depression, pain, sleep disturbances and cognitive dysfunction [80].

Due to the impact of lupus and cytotoxic therapies on reproductive function, women suffering from this disease may have serious concerns and anxiety if their fertility is jeopardized. In fact, women with SLE have fewer children on average than other women.

A very recent survey analyzed the roles of infertility, pregnancy loss, and personal choice on family size in women with RA and SLE. A reproductive history questionnaire was completed by women with RA and SLE participating in a longitudinal observational study. Within each disease cohort, participants were divided into 3 groups: those interested in having children at symptom onset that had either fewer children than planned (group A) or the same number as planned (group B), and those no longer interested in having children at diagnosis (group C). Of the 578 RA and 114 SLE women surveyed, >60% were in group C. Of those interested in having children, 55% with RA and 64% with SLE had fewer children than originally planned. Among women with RA, group A had 1 less pregnancy, 1 less live birth, and an infertility rate 1.5 times higher than group B; the miscarriage rate was similar in both groups. Compared to SLE group B, SLE group A had a similar number of pregnancies, but a 3-fold higher rate of miscarriage and fewer live births. Concerns about child health and personal welfare were found to be associated with a lower pregnancy rate [81].

Summary and Evidence-Based Recommendations

The following guidelines can be useful in the management of women with systemic lupus erythematosus who are concerned about their fertility and pregnancy outcomes.

- Every female patient with SLE should be informed that:

This disease is a multisystemic chronic auto-immune disease that affects almost every organ;

Depending upon the magnitude of the organ involvement and activity of the disease, ovarian dysfunction, menstrual irregularities, infertility and poor obstetric outcomes occur more frequently in this disease even before exposure to cytotoxic immunosuppressive chemotherapies.

- Every women at reproductive age should be counseled with an reproductive endocrinologist to discuss about possible fertility preservation options if their disease are moderate/severe and with complications such as vasculitis and lupus nephritis necessiating the use of cytotoxic therapies detrimental to the ovaries.
- The patients with mild disease and normal reproductive function and who are not interested currently in becoming pregnant should also be informed about the future risk of disease flare and complications, which may compromise their fertility and pregnancy outcomes since a proportion of these patients might be willing to have children in the future. This will help them to decide to consider an appropriate fertility preservation option for now such as embryo and oocyte freezing.
- Every pregnant patient with SLE should be regarded as a high-risk pregnancy and be followed by an obstetrician knowledgeable in high-risk pregnancies
- Maternal health and fetal development should be monitored frequently during pregnancy.
- The flares of the disease, lupus nephritis, hypertension prior to or during pregnancy substantially increase the risks of adverse pregnancy outcomes such as fetal loss, IUGR, preeclampsia and preterm birth.
- At initial and each visits the following tests should be done to assess the extent of the disease during pregnancy

Physical examination, including blood pressure

Renal function (glomerular filtration rate, urinalysis, urine protein/urine creatinine ratio)

Complete blood count

Anti-Ro/SSA and anti-La/SSB antibodies

Lupus anticoagulant (LA) and anticardiolipin antibody (aCL) assays

Anti-double stranded DNA antibodies

Complement (CH50, or C3 and C4)

Uric acid level

- Mycophenolate should not be used during pregnancy. It is listed as a category D drug (positive evidence of risk) for use in pregnancy by the FDA due to increases in both first trimester pregnancy loss and congenital malformations. Instead azothiopurine should be used prior to or during pregnancy.
- Cyclophosphamide is absolutely contraindicated during pregnancy, unless there is no alternative available for life-threatening disease affecting the mother. Fetal loss is a likely outcome of cyclophosphamide administration during pregnancy, as a result of cyclophosphamide toxicity, severe disease, or a combination these factors.
- Methotrexate is teratogenic and should not be used during pregnancy.

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