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Infertility in systemic lupus erythematosus: what rheumatologists need to know in a new age of assisted reproductive technology

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To cite: Stamm B, Barbhaiya M, Siegel C, *et al*. Infertility in systemic lupus erythematosus: what rheumatologists need to know in a new age of assisted reproductive technology. *Lupus Science & Medicine* 2022;**9**:e000840. doi:10.1136/lupus-2022-000840

Received 10 October 2022
Accepted 12 November 2022

Check for updates

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ABSTRACT

Fertility is often a concern for women with SLE. In addition to known indirect factors that influence the ability of a woman with SLE to become pregnant, such as cytotoxic agents, other medications, advanced age and psychosocial effects of the disease, direct disease-related factors are believed to influence fertility. These include diminished ovarian reserve, menstrual irregularities (a function of disease activity) and the presence of antiphospholipid antibodies. The question of whether SLE intrinsically affects fertility, however, remains unanswered. In this review, we address known factors affecting fertility, assess current data regarding a direct impact of SLE on fertility and evaluate potential disease-related risk factors. We focus primarily on studies measuring anti-Müllerian hormone and antral follicle count, the most widely measured markers of ovarian reserve. Our goal is to provide information to rheumatologists faced with counselling patients with SLE regarding their fertility, family planning and options for assisted reproductive technologies, which now include fertility preservation through oocyte cryopreservation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fertility is a concern for women with SLE.
⇒ Important indirect factors that influence fertility and family size in SLE include cytotoxic agents, other medications, advanced age and psychosocial effects of the disease.
⇒ Direct disease-related factors have been suggested to influence fertility but are less well studied.

WHAT THIS STUDY ADDS

⇒ This narrative review synthesises available evidence on a potential direct impact of SLE on fertility.
⇒ Most but not all published data suggest diminished ovarian reserve is more common in women with SLE, with some work suggesting a negative impact of increased disease activity and menstrual irregularities.
⇒ This work presents a concise summary of fertility in SLE, reviews safety of ovarian stimulation cycles in women with SLE and/or antiphospholipid antibodies and presents current options to extend fertility.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given this information, rheumatologists will be better able to counsel patients with SLE regarding their fertility, family planning and options for assisted reproductive technologies, advanced significantly in recent years to include fertility preservation through oocyte cryopreservation.

INTRODUCTION

SLE predominantly affects women of childbearing age, making reproductive health issues an important consideration for rheumatologists who provide comprehensive care. Infertility as an aspect of SLE-related reproductive health is understudied, but of greater interest as assisted reproductive technology (ART) methods become increasingly sophisticated and more widely available. Here, we describe current knowledge regarding prevalence and risk factors for infertility in women with SLE and the available ART options. Detailed recommendations for assessment and management of women with SLE and/or antiphospholipid syndrome (APS) during ovarian stimulation and in vitro fertilisation (IVF) cycles are included in the American College of Rheumatology Guideline for the management of reproductive health in rheumatic and musculoskeletal diseases.[1]

DEFINITION AND ASSESSMENT OF INFERTILITY

Infertility is defined as the inability of a woman to become pregnant after 12 months of unprotected sex.[2] The term subfertility is sometimes used interchangeably with infertility or may refer to any degree of diminished fertility.[3] Infertility is common: in the USA, approximately 10%–15% of couples attempting to conceive experience infertility due to female and/or male factors;

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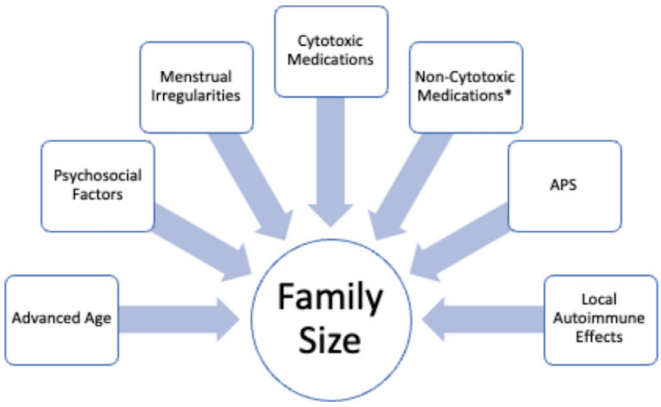

Figure 1 Factors suggested to impact family size in women with SLE. *Non-steroidal anti-inflammatory drugs and high-dose corticosteroids. APS, antiphospholipid syndrome.

endocrine, anatomic, genetic or behavioural changes or for unidentified reasons.[4] A large multinational study of infertile couples conducted by WHO found that female factors were causative in 37% of cases, male factors in 8% of cases and male and female factors combined in 35% of cases.[5] Male factor infertility is usually caused by abnormal ejection of semen, absence or inadequate quantity of sperm or abnormal sperm morphology or motility. Causes of female infertility include abnormalities in the ovaries, uterus, fallopian tubes and endocrine system.[6] Progesterone, thyroid function, prolactin and measures of ovarian reserve are tests commonly used to evaluate female infertility. Imaging studies and procedures include ultrasound, sonohysterography, hysterosalpingography, hysteroscopy or laparoscopy to assess uterine anatomy, tubal patency or presence of endometriosis.

Ovarian reserve, which predicts fertility, is defined as the functional capacity of the ovary (ie, remaining oocyte quantity and quality) . Oocyte quality is the potential for a fertilised oocyte to result in a live-born infant.[7] Biochemical tests to measure ovarian reserve include follicle-stimulating hormone (FSH), estradiol, inhibin B and anti-Müllerian hormone (AMH). Ultrasonographic measures include antral follicle count (AFC) and ovarian volume (OV).[7] Studies that reflect ovarian reserve, including in SLE, report AFC and AMH levels.[8 9] Unlike FSH, levels of AMH, which is secreted by follicle granulosa cells, remain relatively stable throughout the menstrual cycle and are more sensitive and specific than other biochemical measures. Values for fertile women range from 1.0 to 3.5 ng/mL; values <1.0 ng/mL suggest reduced ovarian reserve.[7] AMH testing is simpler to conduct; multiple studies suggest AMH and AFC are equal in predicting ovarian reserve.[7 10] OV is a less sensitive marker than AMH or AFC and has intercycle and intracycle variability.[7]

FERTILITY IN WOMEN WITH SLE

Infertility may be more common in women with SLE than suspected. In an evaluation of 136 infertile women, 1.5% had undiagnosed SLE.[11] Overall, women with SLE have fewer children than do healthy women,[12 13] possibly related to the known higher risk of pregnancy loss. While SLE pregnancy outcomes have improved in recent years, an increased risk of pregnancy complications, including loss, persists.[14–16] In a recent meta-analysis of pregnancy studies published from 2017 to 2019, patients with SLE had markedly increased risk of stillbirth (risk ratio (RR) 16.49, 95% CI 2.95 to 92.13; p=0.001) and fetal loss (RR 7.55, 95% CI 4.75 to 11.99; p=0.00001).[14] In contrast, although it has long been assumed that women with SLE have no difficulty becoming pregnant, growing evidence suggests the diagnosis of SLE itself may affect the ability to conceive and impact family size.

Indirect factors

Indirect causes of infertility or subfertility that may affect women with SLE include cytotoxic and other medications, ageing and psychosocial effects of the disease (see figure 1). Monthly intravenous cyclophosphamide (CYC) may induce premature ovarian failure (POF) by causing follicular death of rapidly dividing granulosa cells.[17–19] POF is defined by premature amenorrhoea lasting a minimum of 4 months, hypoestrogenism and persistent elevated gonadotropin levels in women <40 years of age.[18 19] Primary ovarian insufficiency, increasingly used instead of POF, is potentially more accurate because it includes cases where ovaries may be capable of hormone production and ovulation. A recent systematic review and meta-analysis confirms CYC treatment and cumulative dose as the most significant predictors of POF in women with SLE[20]; patients with SLE receiving higher cumulative doses had twice the risk of POF than those receiving lower cumulative doses. Concurrent treatment with gonadotropin releasing hormone agonist (GnRH-a) therapy reduced the POF risk of standard monthly CYC.[20] Underlying genetic metabolic differences also may contribute: studies of women with lupus nephritis treated with CYC showed the allele CYP2C19*2 to be protective against POF.[21] As estimated by AMH levels, the lower-dose EURO-lupus CYC protocol (six fortnightly pulses at a fixed dose of 500 mg) does not appear to impair ovarian reserve.[22]

Because the less gonadotoxic alternative mycophenolate mofetil (MMF) is now commonly prescribed, intravenous CYC use is less frequent,[23] although treatment with CYC remains standard of care for life-threatening SLE. Several clinical studies that compared CYC with other immunosuppressive drugs for association with menstrual irregularities and ovarian insufficiency confirmed that CYC alone appears to have a significant effect. In 216 patients with SLE exposed to CYC, MMF, azathioprine (AZA) or calcineurin inhibitors, mean levels of serum AMH were lower in women treated with CYC compared with non-CYC-treated women. Mean AMH levels in those treated with MMF, AZA or calcineurin inhibitors were no different than in untreated women with SLE.[24]

Other medications commonly used by patients with SLE may influence fertility transiently through alternate

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mechanisms. When taken regularly, non-steroidal anti-inflammatory drugs can contribute to infertility in patients with SLE by causing luteinised unruptured follicle syndrome that inhibits ovulation.[12] High-dose corticosteroids may also contribute to menstrual abnormalities in patients through interference with the hypothalamic-pituitary-ovarian axis.[25]

Advancing age diminishes ovarian reserve and reduces the likelihood of conception.[26] Many women, diagnosed with SLE during their early reproductive years, may be advised to defer pregnancy until disease activity remits.

Finally, the physical and emotional experience of living with SLE may influence psychological well-being. Patients with SLE experience lower self-esteem and higher rates of depression than healthy comparators.[27 28] Diminished libido and physical limitations of the disease may reduce intercourse frequency, indirectly affecting likelihood of pregnancy.[13 29] Concerns about personal health (including the ability to care for a child) and health outcomes of unborn children may impact decision making and contribute to a smaller family size.

Other factors suggested, but not proven to affect ovarian reserve in the general population have not been studied in women with SLE: low levels of vitamin D, low levels of antioxidants and extremes of body mass index (BMI).[30–32] Low serum vitamin D directly correlates with lower AMH levels in the general population.[28] Serum vitamin D levels are lower in women with SLE than in healthy controls.[33] SLE is associated with elevated production of free radicals (reactive oxygen species) and oxidative stress,[34 35] the latter proposed to play a fundamental role in infertility in a general population.[30] Despite limited evidence that use of oral antioxidants improves outcomes in subfertile women, supplementation is commonly advised. Individuals at the lowest and highest ends of the BMI spectrum experience increased risk of infertility.[31] Evidence of an association between SLE and obesity is limited[36]; however, both comorbid obesity and very low BMI could increase risk for infertility. Whether supplements[37] or optimisation of BMI improve the chances of conception for subfertile women, including those with SLE, remains unknown.

Direct disease-related factors

Ovarian reserve

It is not clear whether AMH and AFC are diminished in non-CYC-treated patients with SLE and, if so, whether there is a correlation with SLE disease activity or other disease-specific factors. Several studies suggest impaired intrinsic fertility (reduced AMH levels) among women with SLE independent of gonadotoxic therapy (table 1). One prospective study that compared 33 premenopausal patients with SLE with mild disease activity and no CYC exposure to 33 age-matched healthy comparators found that patients with SLE had lower AMH levels.[38] There was no correlation between AMH and either duration of illness or disease activity measured by the SLE Disease Activity Index (SLEDAI). In another case-control study of 40 women of childbearing age with SLE with no history of previous immunosuppressive medication use, mean AMH level in women with SLE was lower than that of healthy controls . In this study, AMH and SLEDAI scores were inversely correlated. Furthermore, within the SLE group, patients with regular menstruation had significantly higher AMH levels than did those with irregular cycles and/or abnormal bleeding patterns.[10] In a recent cross-sectional study, 68 African-American women with SLE never exposed to CYC were 1.5-times more likely to have AMH levels below the 25th percentile when compared with women without SLE, even when controlling for other relevant factors such as BMI and use of hormonal contraception (prevalence ratio 1.55, 95% CI 0.97 to 2.47).[39]

A prospective controlled study compared 20 non-CYC-treated patients with SLE with 20 age-matched healthy controls using transvaginal ultrasonographic measures of ovarian reserve. Patients with SLE had reduced OV and AFC and rates of higher menstrual irregularity.[40]

Published data conflict. A cross-sectional study comparing 86 patients with SLE and 44 age-matched healthy comparators, which included only patients with SLE with regular menstrual cycles, did not find differences in AMH serum levels. AMH levels were lower in patients with SLE with major organ involvement than in healthy controls, but results were not statistically significant. Patients with SLE with mild disease (primarily articular and/or cutaneous involvement) and healthy comparators had comparable AMH levels.[41] Another case-control study did not find a difference in AMH levels between 40 patients with SLE and 40 healthy controls,[9] nor did AMH levels correlate with any other measured factors including disease duration (r=0.2; p=0.3), BMI (r=0.2; p=0.2), disease activity measured by SLEDAI (r=0.1; p=0.7) or damage measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (r=0.1; p=0.7). No associations were found between AMH and ethnicity or non-CYC immunosuppressive medications. Surprisingly, there was also no association with use of CYC or with current smoking, both of which are considered risk factors for subfertility.

Abnormal uterine bleeding

Uterine bleeding of abnormal quantity, duration or schedule is more frequent among women with SLE, with a higher risk for irregular or reduced uterine bleeding among those treated with CYC.[17] Although the relationship between irregular uterine bleeding and ovarian reserve is difficult to discern, changes in the menstrual cycle may influence timing and likelihood of pregnancy. Women with SLE are more likely to have menstrual disturbances, in particular sustained amenorrhoea: in a study comparing 61 patients with SLE with 120 healthy controls, the prevalence of a menstrual disorder was three times higher in patients with SLE (49.2%) vs healthy control counterparts (16.7%) and was highest in those >30 years old and those on CYC therapy.[17]

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Table 1 Markers of ovarian reserve in SLE

Study	Type of study	No. CYC-untreated (CYC–) patients with SLE	Measure of ovarian reserve AMH	AFC	OV	Results	Comments
Gasparin *et al*[9]	Case-control	40	√	–	–	Comparable AMH levels in SLE/CYC– and control groups.	
Gao *et al*[10]	Case-control	40	√	–	–	AMH of SLE/CYC– group was significantly lower than in control group (p<0.001).	AMH was negatively correlated with disease activity (SLEDAI) (p=0.033). AMH concentration in SLE/CYC– group with normal menstruation was higher than SLE/CYC– group with abnormal menstruation (p<0.001).
Angley *et al*[39]	Cohort	68	√	–	–	SLE/CYC– women were 1.5–1.6 times more likely to have AMH levels <1.0 ng/mL (PR 1.62, 95% CI 0.93 to 2.82) and AMH levels below the 25th percentile as compared with women without SLE (PR 1.55 (95% CI 0.97 to 2.47)).	
Lawrenz *et al*[38]	Cross-sectional	33	√	–	–	AMH of SLE/CYC– group was significantly lower than in control group (p<0.05).	There was no correlation between AMH and illness duration or disease activity (SLEDAI).
Ulug *et al*[40]	Cohort	20	–	√	√	AFC and OV of SLE/CYC– group were significantly lower than in control group (p<0.001, p=0.006, respectively).	Menstrual irregularities significantly higher in SLE/CYC– group than in control group.
Di Mario *et al*[41]	Cross-sectional	86	√	–	–	Comparable AMH levels in SLE and control groups.	

AFC, antral follicle count; AMH, anti-Müllerian hormone; CYC, cyclophosphamide; OV, ovarian volume; SLEDAI, SLE Disease Activity Index.

Confirming that disease activity independently contributes to menstrual disturbances is challenging since high disease activity and medical treatments with corticosteroid and cytotoxic therapy often co-occur. Corticosteroid therapy can suppress the function of the hypothalamic-pituitary-ovarian system, reducing levels of luteinising hormone and FSH, and cytotoxic drugs increase risk of amenorrhoea and ovarian insufficiency. Some studies do support an independent effect of disease activity on menstrual cycle pattern.[42–44] Fifty-four per cent of patients with SLE experienced menstrual cycle disorders, predominantly oligomenorrhoea, in one cohort of 94 women (15% of whom were untreated).[42] Frequencies of menstrual cycle disorders and SLEDAI score were positively correlated among patients without prior or current treatment with cytotoxic therapy or high-dose corticosteroid (p=0.001). Decreased progesterone levels and hyperprolactinaemia have also been associated with higher SLEDAI scores among patients with SLE without such prior or current treatment, further suggesting that ovarian function in patients with SLE may be independently associated with disease activity.[43] In a separate study of 36 patients with SLE not treated with cytotoxic therapy, 53% experienced menstrual irregularities and SLEDAI score correlated with the presence of a menstrual irregularity (p=0.02).[44] Furthermore, the patients with menstrual irregularities were significantly more likely to have SLEDAI >8 as compared with patients with SLE with normal cycles (p=0.008).

Intriguing but limited data support an autoimmune aetiology for some cases of POF in the general population, with autoimmune oophoritis leading to ovarian damage and resulting POF. Like the pathology seen in other autoimmune endocrinopathies, antibodies against steroid-producing cells as well as oophoritis with $CD4^+$ and $CD8^+$ T lymphocyte infiltration have been reported.[45] While association with SLE is poorly studied, anticorpus luteum antibodies have been detected in sera of patient with SLE[46]; one study suggested an association of amenorrhoea with presence of anticorpus luteum antibodies and elevated FSH levels in patients with SLE.[47]

Antiphospholipid antibodies

APS is a systemic autoimmune disease that occurs alone or in association with other rheumatic diseases, usually SLE; clinical manifestations include arterial and venous

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thrombosis and pregnancy morbidity.[48] Whether there is a relationship between antiphospholipid antibodies (aPL) and female infertility, and what mechanisms may be involved, remains poorly understood.[49] aPL are detected by functional coagulation (lupus anticoagulant (LAC)) or solid phase (anticardiolipin (aCL) and anti-β2 glycoprotein I (anti-β2GPI)) assays.[50] Recognised pregnancy complications and poor reproductive outcomes include spontaneous abortion, fetal loss, stillbirth, premature birth, small for gestational age infants and pre-eclampsia.[51]

While recognised as a risk factor for fetal loss and other adverse pregnancy outcomes, aPL also have been suggested to impact fertility by influencing fertilisation and implantation early in the reproductive process.[12] Binding of aPL to antigen may be responsible for the degradation of phospholipid adhesion molecules between different trophoblast elements; additionally, aPL have been suggested to hinder implantation via a direct influence on placental growth and function.[52] To date, there is no consensus on impact of aPL regarding general infertility or IVF failure.[52–54] A recent comprehensive review, however, concluded that there were inadequate data to support routine aPL testing in patients with infertility in the general population,[54] and another recent study found no association of IVF success with either the presence or number of aPL in 173 patients.[53] Currently, the American Society for Reproductive Immunology does not recommend testing or treating for aPL in women with repeated failed IVF cycles.[55]

SLE AND ASSISTED REPRODUCTIVE TECHNOLOGY

When fertility is impaired in women with SLE for any reason, ART may be necessary to achieve pregnancy. Assuring the safety of such elective procedures in patients with SLE, especially those with positive aPL or APS, is a primary concern and requires guidance from both rheumatology and reproductive endocrinology and infertility (REI) specialists.

ART procedures have significantly evolved in terms of both safety and success rates. Procedures vary, but often include ovarian stimulation, oocyte retrieval, IVF and transfer of the fertilised embryo into the uterus. Once oocytes are retrieved—usually through transvaginal puncture following ovarian stimulation—they may be frozen or fertilised through incubation with sperm or intracytoplasmic sperm injection. Following fertilisation and incubation, the embryo may be transferred into the woman's uterus during either the cleavage stage (2–3 days postretrieval) or the blastocyst stage (5–6 days postretrieval). In recent years, blastocyst transfer has become most common; blastocysts may also be frozen and transferred later in a non-stimulated cycle.[56] Protocol changes have decreased both risk and severity of ovarian hyperstimulation syndrome (OHSS), where cystic enlargement of the ovaries results in fluid shifts from the intravascular to the third space due to increased capillary permeability.[57] For some patients, guidance from preimplantation genetic testing of embryos prior to transfer can improve the likelihood that the transferred euploid embryos result in successful implantation, clinical pregnancy and live birth.[58]

Ovarian stimulation is generally considered to be safe in patients with SLE if disease is clinically inactive and prophylactic anticoagulant medications are administered when indicated.[59] The ACR reproductive health guideline details assessment and management of patients with SLE and aPL-positive patients for ART.[1] All patients with SLE should be assessed for disease activity and ART deferred for those with moderate or severe disease activity. If immediate embryo transfer is planned, patients should be on pregnancy-compatible medications. Prophylactic corticosteroid to prevent flare is not generally recommended.

aPL status should be determined prior to ovarian stimulation. The ACR guideline uses APS classification criteria to define a positive aPL test: positive LAC, positive aCL (IgG or IgM >40 units) or positive anti-β2GPI (IgG or IgM >99%).[48] Recommendations for low titre or 'non-criteria' aPL are not provided; for these patients, therapy decisions should be based on clinical and laboratory history and physician-patient discussion. For classification criteria-positive aPL patients, treatment with low molecular weight heparin (usually enoxaparin) during the stimulation cycle is recommended. For aPL-positive patients with no obstetric or thrombotic history, the recommendation for prophylactic enoxaparin 40 mg subcutaneously daily is conditional; that is, the decision to proceed is based on individualised patient-physician discussion. For aPL-positive patients meeting classification criteria for obstetric APS, prophylactic enoxaparin (40 mg subcutaneously daily) is strongly recommended; for those meeting APS classification criteria for thrombotic APS, therapeutic enoxaparin (1 mg/kg two times per day subcutaneously) is strongly recommended. Enoxaparin is generally held 24 hours prior to oocyte extraction and resumed within 12–24 hours. If pregnancy is not achieved, or if oocytes or embryos will be frozen, then enoxaparin is discontinued after 7–10 days.[1]

Published reports confirm the relative safety of ovarian stimulation and IVF in women with SLE and/or APS, with the lowest rates of adverse events in the most recently reported series.[60 61] While there are risks, including SLE flare and thrombosis, complications are infrequent.[2] IVF-induced thromboses have often occurred in the context of OHSS; however, incidence and severity of OHSS have decreased dramatically with current protocols using GnRH-a rather than human chorionic gonadotropin to trigger final oocyte maturation.[62] In a single-centre review of 97 procedures in 37 women with SLE and/or APS, the overall complication rate was 8%, with 4 SLE flares and 4 thromboses; furthermore, half of the complications were in patients who prematurely discontinued medications, and no patient developed OHSS.[60] Similarly, another recent multicentre study of 58 cycles in 28 women with SLE and/or APS reported only 3 lupus flares (including 1

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in a woman who self-discontinued medication) and 1 case of OHSS with no thromboses.[61]

Successful oocyte cryopreservation is the most recent significant innovation in ART, increasingly used for both medical and social reasons. Early attempts at oocyte cryopreservation used a slow cooling procedure with limited success. Use of vitrification (a rapid freezing technique) has improved outcomes so that frozen oocytes have IVF success rates equal to those of fresh oocytes. In 2012, the Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology determined oocyte cryopreservation was no longer experimental[63]; since then, rates of elective oocyte freezing have increased yearly.[64] Most centres recommend freezing before age 35 years when possible: the maternal age at freezing strongly affects likelihood of later successful embryo formation and successful pregnancy. However, studies suggest that women often underestimate the effect of age on future fertility.[65] Social advantages of egg freezing are obvious: women may preserve their fertility to pursue career goals, achieve financial security or find a desirable partner.

Medical oocyte cryopreservation is currently offered as fertility preservation to young cancer patients facing gonadotoxic therapy.[66] Patients with SLE, especially those without a long-term partner, may have both medical and social incentives to pursue oocyte cryopreservation. For many patients, cryopreserved oocytes would increase options regarding pregnancy planning with respect to disease-related activity and age-related fertility decline. A woman requiring therapy with pregnancy-incompatible medications such as MMF or methotrexate (but not CYC) may continue medication and safely undertake egg freezing without concern for teratogenic effects,[1] preserving her potential for biological offspring in the future when she no longer requires these medications. Patients with SLE are counselled to pursue pregnancy during periods of quiescent disease, which may lead to deferred pregnancy plans and older age with reduced fertility when disease quiescence is finally achieved. While availability of oocyte cryopreservation is still limited in terms of access to specialists and insurance coverage, it is hoped that availability will increase in coming years particularly for medical considerations beyond cancer.

Other ART-related procedures offer additional options in family planning for some patients. While not studied specifically in patients with SLE, donor egg use is an effective fertility therapy and has been simplified by availability of oocyte cryopreservation; previously, egg donation required fresh oocytes, making timing of the procedure more complicated. Some women with POF or age-related fertility decline who are unable to successfully conceive with IVF may choose to pursue this option for a successful pregnancy. Finally, for women with disease-related damage such as pulmonary hypertension, cardiomyopathy or severe renal insufficiency that precludes pregnancy due to maternal risk, use of a gestational carrier may be an option, although potentially limited by financial, legal, cultural and other factors.

FUTURE DIRECTIONS

Family planning is an important component of quality of life for most women. Understanding of pregnancy in SLE has improved after decades of research, yielding identification of important risk factors and improved outcomes. In contrast, fertility in SLE remains poorly understood, infrequently studied and rarely discussed. A direct effect of SLE on fertility in women of childbearing age is unproven; however, data do suggest that, aside from known risk factors of cytotoxic medications, advanced age and psychosocial disease effects, certain disease characteristics such as SLE activity may also impact the ability to conceive. Well-designed, large-scale studies could help confirm or refute this finding and identify the most important risk factors for infertility. This would assure targeted screening of ovarian reserve and counselling where needed. Just as importantly, however, the inevitable age-related decline in fertility—especially in the context of ongoing lupus activity—is likely to be the most common factor limiting the opportunity for pregnancy. Rheumatologists and patients with SLE should be aware of both these fertility issues and the advances in reproductive medicine that may extend female fertility.

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Contributors BS, LS and MB all provided substantial contributions to the conception and design of this narrative review, the acquisition, analysis and interpretation of data for the review and drafting of the manuscript. BS, LS, MB, CS, SL and ML all revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The two authors who do not appear on the search (above) are: BS bcs2152@alum.barnard.edu and CS (coauthor) siegelc@hss.edu.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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