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Lupus (S Keeling, Section Editor)

Reproductive Issues in Males with SLE

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Opinion statement

Purpose of review Sexual function and fertility are neglected topics in men with systemic lupus erythematosus (SLE) in the literature. This review examines the impact of SLE and its treatment on fertility and erectile function.
Recent findings Systemic illness, such as chronic kidney disease, and drugs used in SLE are associated with male infertility and sexual dysfunction through changes at the level of the hypothalamic-pituitary axis and direct testicular damage. In SLE patients, evidence shows a dose-dependent gonadotoxicity associated with intravenous (IV) cyclophosphamide (CYC). In contrast, recent observational studies evaluating disease-modifying anti-rheumatic drugs, non-steroidal anti-inflammatory drugs, and corticosteroids have found little evidence suggesting a significant impact of paternal exposure on fertility or pregnancy outcomes. In most patients, infertility management is focused on controlling SLE disease activity, minimizing the dose of gonadotoxic medications and cryopreserving sperm prior to treatment with IV CYC.
Summary Reproductive issues are not uncommon in males with SLE. Understanding the impact of disease activity and drug effects on reproductive health may avert irreversible infertility and improve patient quality of life. However, additional studies are required to further explore the impact of SLE and its treatment on male fertility.

Introduction

Males represent approximately 10% of patients with systemic lupus erythematosus (SLE). Studies evaluating sex differences in SLE are not consistent, but several groups have identified a more severe disease course and higher rates of renal involvement in men compared to women [1–4]. The reported mean age at diagnosis in men ranges between 26 and 55 years, with Caucasians having an

older age of onset compared to subjects from other race/ethnicity [4].

Sexual function and fertility are neglected topics in men with SLE in the literature. However, sexual dysfunction and infertility, which can have a variety of aetiologies in males with SLE, could potentially adversely impact the quality of life in affected men. Hypogonadism in males is characterized by the disruption of testosterone and/or sperm production by the testes. It can result from disease of the testes (i.e., primary hypogonadism) or disease of the hypothalamus/pituitary (i.e., secondary hypogonadism), which can be distinguished by measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), and inhibin B levels. While male fertility naturally begins to decline with age, in patients with SLE, sexual dysfunction and infertility can arise precociously from disruption at any level of the hypothalamic-pituitary-gonadal (HPG) axis.

Systemic illnesses, especially chronic kidney disease and the use of alkylating agents to control disease activity, are associated with male infertility. Other medications commonly used in the management of SLE are potential teratogens and may lead to adverse pregnancy outcomes when used in females. Paternal use, however, appears to be safer without significant impact on fertility, though current guidelines recommend discontinuing most immunosuppressives several weeks prior to conception.

The current report reviews the effects of SLE and its treatment on male fertility and sexual function.

Impact of SLE disease activity and/or damage on fertility and sexual function

The HPG axis is highly sensitive to the stress of acute or chronic disease. In SLE, high gonadotropin levels and hypoandrogenism are frequently described [5–7]. A comprehensive study by Soares et al. identified 35 SLE patients aged 15–45 years and compared them to healthy age-matched controls [8]. The patients underwent thorough gonadal evaluation and were found to have markedly diminished median testicular volumes in addition to greater abnormalities in sperm motility, concentration, and morphology compared to controls. Additionally, only 7 (20%) SLE patients fathered children after disease onset, compared to 28 (80%) controls. The authors also noted that lower testicular volumes, higher levels of FSH, and treatment with intravenous (IV) cyclophosphamide were associated with more severe semen abnormalities. In a follow-up study, the levels of inhibin B, a peptide inhibitor of FSH secreted by the Sertoli cells in the seminiferous tubules, were found to be markedly reduced in SLE patients [9]. The results revealed that semen abnormalities in lupus patients were strongly associated with low inhibin B levels, suggesting that seminiferous tubule dysfunction is potentially secondary to SLE-induced and/or drug-related testicular damage.

In addition, several studies have revealed that men with SLE are more likely to develop anti-sperm antibodies [10, 11]. Though these antibodies might potentially induce damage to the seminiferous tubules, their impact on fertility remains unclear, as they have also been identified in a significant portion of fertile men.

Lupus nephritis is a frequent and serious manifestation of SLE and its prevalence varies significantly (12–69%) depending on the study population [12]. Importantly, clinical renal disease appears to be more common and of worse prognosis in males than in females [13, 14]. Chronic renal failure in males is associated with decreased fertility through impaired spermatogenesis and sexual dysfunction. Measurable changes to the hypothalamic-pituitary axis appear with only moderate reductions in the glomerular filtration rate (GFR) and intensify as

kidney dysfunction progresses. Defects in spermatogenesis and fertility are thought to result from a state of functional gonadotropin deficiency or resistance rather than a direct cytotoxic effect of uremia with associated testicular damage [15, 16]. Moreover, erectile dysfunction can result from arterial and veno-occlusive insufficiency, in addition to hormonal imbalances such as hyperprolactinemia, both of which are more prevalent in patients with renal insufficiency [17].

Antiphospholipid syndrome (APS) is a well-known risk factor for fetal loss in females with SLE, but its impact on male fertility is mostly unknown. One study compared 10 male SLE patients with APS to 20 age-matched healthy controls and found that SLE-APS patients reported a higher rate of erectile dysfunction (30 vs 0%, respectively) and were more likely to have abnormal sperm count, motility, and morphology [18]. However, subgroup analysis revealed that the difference in sperm quality was attributable to IV cyclophosphamide use in patients who had concomitant lupus nephritis. Accordingly, APS may have an impact on erectile function but disease effect on fertility remains unclear.

Finally, males with SLE are more likely than the general population to have sex chromosome aneuploidies (i.e., abnormal number of sex chromosomes) with associated hypogonadism and testicular failure. Recently, a large study by Dillon et al. evaluated 316 men with SLE and identified 3 Klinefelter karyotypes, 4 mosaic Klinefelter karyotypes, and 1 XX male karyotype (X chromosome carrying the sex-determining *SRY* gene normally found on the Y chromosome), whereas no sex chromosome aneuploidies were identified in the control population [19]. Given that one of the hallmarks of Klinefelter's syndrome is primary hypogonadism with azoospermia [20], most of these patients, including mosaic karyotypes, are infertile, though fertility can be achieved with assistive reproductive technology.

Effect of medications on fertility and sexual function

Cyclophosphamide

Cyclophosphamide (CYC) is the most commonly prescribed cytotoxic alkylating agent in rheumatic diseases, though most large data sets evaluating the gonadal toxicity of CYC are derived from studies in patients being treated for nephrotic syndrome or malignancies. CYC interferes with DNA repair mechanisms and dose-related gonadal toxicity, which can result in long-term infertility, is a well-studied adverse effect. One meta-analysis evaluated the gonadal impact of CYC in 116 men treated with CYC as a single agent for renal disease with a mean total dose of 395 mg/kg [21]. Primary hypogonadism was identified in sexually mature men with cumulative doses as low as 100 mg/kg, and this risk increased to >80% with doses in excess of 300 mg/kg. Prepubertal boys were less affected as only 10% had gonadal dysfunction when receiving less than 400 mg/kg (total dose) of CYC. Another meta-analysis evaluating children and adolescents treated with cytotoxic therapy for relapsing nephrotic syndrome also identified a marked increase in the risk of azoospermia with cumulative doses of CYC exceeding 300 mg/kg. In many cases, CYC-induced infertility may be reversible, though recovery appears unpredictable and can take up to 4 years [22]. Similarly, Soares et al. found that SLE patients treated with IV CYC (n = 14)

had lower testicular volumes, total sperm count, and total motile sperm when compared to SLE patients not treated with IV CYC (n = 21) (4).

IV CYC appears to be the most important cause of infertility in lupus patients. Accordingly, reducing the cumulative dose of IV CYC by, for example, adhering to the lower dosing regimen (500 mg every 2 weeks for a total of six doses) established by the ACCESS and Euro-Lupus Nephritis trials when possible (e.g., based on disease severity and patient race/ethnicity) could potentially help preserve fertility in men with SLE [23•, 24]. Additionally, when possible, sperm cryopreservation should be offered to postpubertal males prior to the initiation of IV CYC therapy [25, 26•, 27]. Fertility outcome studies in male cancer survivors reveal live pregnancy rates of up to 49% when cryopreserved semen is coupled with assistive reproductive technologies.

In younger SLE males who have not yet undergone spermatogenesis, sperm banking is not an option and experimental protocols are being developed that include the cryopreservation of spermatogonial stem cells for future autologous intra-testicular transplantation [28]. However, despite achieving successful restoration of fertility in animal models, human data is lacking [29]. Other alternatives for preserving fertility such as gonadal protection with testosterone have not been shown to be effective.

In females, CYC appears to have significant teratogenicity especially when administered in the first trimester of pregnancy. In males, however, there is only sparse data regarding the outcome of children born to men treated with CYC. These reports are anecdotal [30] and no experimental evidence exists to support a direct relationship between paternal CYC treatment and an increased risk of congenital anomalies [31, 32].

Methotrexate

Methotrexate (MTX) is a folate antagonist and remains a commonly used immunosuppressive in SLE. In the context of malignancy, when used as part of a chemotherapeutic regimen, MTX may induce reversible sterility [33]. The impact on fertility of monotherapy with low-dose MTX (i.e., 25 mg weekly or less) appears to be less significant, though one case report identified oligospermia and sperm abnormalities associated with MTX monotherapy in a young male with severe psoriasis [34]. In this patient, normalization of sperm count and morphology was noted once methotrexate was discontinued. This contrasts with an earlier study which found no effect of low-dose MTX on the fertility parameters of 26 men with psoriasis. Sperm counts and morphology in all 26 patients were unchanged before and after treatment, and testicular biopsies in 5 of the men revealed no histologic abnormalities [35]. Thus, evidence seems to suggest that low-dose MTX monotherapy does not have an appreciable impact on male fertility [36].

Data regarding MTX use and ED is sparser but several case reports indicate a potential association. Both ED and reduced libido are listed by drug manufacturers as very rare side effects of MTX. In all cases, the ED was reversible with cessation or dose reduction of MTX [37, 38].

Recent studies evaluating pregnancy outcomes and paternal low-dose MTX exposure during the time of conception are reassuring. One prospective cohort study examined 113 pregnancies fathered by men on low-dose MTX and found

that the rates of major birth defects and spontaneous abortions were comparable to those of 412 non-exposed pregnancies [39]. These results are concordant with an observational study that found no increased adverse pregnancy outcomes in 49 fathers with inflammatory arthritis (mainly ankylosing spondylitis) exposed to methotrexate within 12 weeks of conception [40•]. In light of these results, it has been suggested that a 3-month MTX-free interval until conception is likely unnecessary in male patients [39]. However, no study to date has assessed the potential effect of MTX (or any other drug used to treat SLE) on sperm DNA structure, which could have a transgenerational health effect.

Azathioprine

Azathioprine is an important agent in SLE treatment. Azathioprine and its active metabolite, 6 mercaptopurine (6MP), are also frequently used in inflammatory bowel disease and solid organ transplant patients. Currently, the few studies investigating the impact of paternal thiopurine exposure reveal that thiopurines do not decrease semen quality [41, 42] and has no obvious negative impact on the rates of congenital anomalies [43]. Therefore, current evidence, although limited, does not support the withdrawal or substitution of these medications in male SLE patients prior to conception.

Mycophenolate mofetil

Mycophenolate mofetil, an agent that blocks de novo purine synthesis in lymphocytes, has become a first-line agent in induction and maintenance therapy of lupus nephritis. Although human data is lacking, mycophenolate mofetil has not been shown to impair the fertility of male rats [44, 45]. Currently, given the teratogenic potential of mycophenolate mofetil associated with maternal exposure, drug manufacturers suggest that sexually active men exposed to mycophenolate mofetil or mycophenolic acid enteric-coated tablets use condoms during treatment and for 90 days or 13 weeks (respectively) after discontinuation. However, two large transplant registry studies (n = 830 and 2463, respectively) examining the impact of paternal exposure to mycophenolate derivatives on pregnancy outcomes have not identified an increased risk of fetal malformations or pregnancy complications compared to the general population [46, 47]. Therefore, despite the theoretical risks of paternal exposure to teratogenic agents, there is little data to support the cessation of mycophenolic acid derivatives in male SLE patients prior to conception. However, further data is needed to fully assess the impact of mycophenolate derivatives on male fertility.

Corticosteroids

Data on the impact of corticosteroids on male fertility is limited and conflicting. Chronic glucocorticoid use has been shown to decrease serum testosterone levels, but its impact on male fertility is less clear [48–50]. In one study evaluating 23 patients with inflammatory bowel disease treated with azathioprine, concomitant therapy with corticosteroids showed no negative impact on semen quality [41]. To date, no data exists on paternal exposure to corticosteroids and pregnancy outcomes.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) remain frequently used for pain control and management of certain SLE manifestations (e.g., arthritis, serositis). One retrospective study examining 1376 men from the general population attending an infertility clinic noted decreased seminal volume, sperm quality, and motility in those chronically exposed to NSAIDs [51]. However, the clinical significance of the data remains unclear given that the exposed group was small and most patients (73%) reported taking only aspirin. One large prospective cohort study (n = 80,966) identified an increased risk of ED with chronic NSAID use (OR 1.22, CI 1.18–1.27) even after controlling for all potential confounding variables [52]. These results corroborated those of an earlier Finnish cohort study which also indicated that the increase in ED was independent from the indication of NSAID use (i.e., disease being treated) [53]. Thus, NSAIDs have been associated with an increased risk of ED but there is little data to suggest a significant impact on male fertility.

Conclusion

In summary, several reproductive issues are of concern in men with SLE. Erectile dysfunction and reduced libido might be more prevalent due to disease-related activity and/or damage, as well as potential drug effects. In addition, CYC is associated with dose-dependent gonadal dysfunction in exposed males. While data are limited, paternal exposure to immunosuppressives does not seem to be associated with adverse pregnancy outcomes. However, further studies of reproductive issues in men with SLE are needed to appropriately counsel male patients regarding the effect of the disease and its treatments on their reproductive health.

Compliance with Ethical Standards

Conflict of Interest

Omid Zahedi Niaki declares that he has no conflict of interest.
Sasha Bernatsky declares that she has no conflict of interest.
Evelyne Vinet declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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