Causes and management of infertility in systemic lupus erythematosus

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Abstract
SLE is a multi-system, autoimmune condition that can influence both male and female fertility. Inability to conceive may be attributed to several factors that may act singly or in combination: (i) older age in patients with SLE compared with healthy controls; (ii) disease-related infertility; and (iii) infertility through gonadotoxic treatments. In addition, psychosocial factors related to the disease may lower fecundity and may be associated with apparent infertility. Many therapeutic avenues are open to counteract reproductive damage in the management of SLE and to assist conception once infertility is diagnosed. These treatments can include the administration of gonadotrophin-receptor hormone analogues while receiving CYC treatment, the use of assisted reproductive technologies, such as in vitro fertilization and psychosocial intervention to promote a healthier relationship with their partner. Knowledge of how these reproductive problems occur and its prevention/treatment in SLE patients should avert irreversible infertility as well as give hope to SLE patients with infertility.

Key words: Systemic lupus erythematosus, Infertility, Spermatogenesis, Amenorrhea, Cyclophosphamide.

Introduction
SLE is a multisystem, autoimmune disease that has a pre-dilection for women of childbearing age [1]. The reproductive system may be affected in women and men, as a result of disease activity and through iatrogenic cytotoxic treatments. Impairment of reproductive capability can be due to: (i) problems preventing successful fertilization thus leading to infertility; (ii) obstacles in effective implantation to the uterine wall; (iii) difficulties in maintaining pregnancy post-implantation; and (iv) complications during labour. The focus of this review is infertility, which has been defined as the inability for a woman to conceive after 1 year of regular, unprotected coitus [2]. Factors that affect fertility in lupus patients and the management of infertility, including the options for treatment will be discussed.

Methods
Literature search
PubMed Medline was screened for all relevant articles published up until the end of 2009, using the search terms: fertility, infertility, lupus, systemic lupus erythematosus, testes, ovaries, spermatogenesis, ovulation, amenorrhea, menstrual and treatment. Articles deemed relevant by examination of their abstracts were retrieved and their bibliographies scrutinized for further relevant papers. A selection of those deemed most important to this field were then included and discussed in this review.

Epidemiology
While there is a general consensus that patients with SLE have a fertility rate comparable to that of the general population, this viewpoint is challenged for several reasons. First, of the 9% afflicted with infertility worldwide [3], SLE contributes to ~1% of infertile patients, which is more than would be expected for a disease that affects ~1 in 2000 adult women [4–7]. There is a known drop in the pregnancy rate once SLE is diagnosed [8]. This fall in birth rate varies across different ethnic groups, but patients of Caucasian ethnic origin with SLE tend to have reduced family size when contrasted to healthy controls [9, 10]. There are numerous causes of infertility secondary to SLE and its treatment [11, 12].
Causes of infertility

Ageing

Fertility is most likely to be comparable to that of the healthy population when patients have mild disease, especially with sufficient disease control and appropriate medications. The effect of ageing on female fertility is detrimental to the success of conception. With age, fertility declines through the progressive loss of ovarian reserve and the poorer quality of oocytes available [13]. In the economically developed world, there has been a demographic drift in deferring pregnancy, often until the late 30s [14]. SLE often presents in this age group [1, 4], especially in Caucasians. Women with lupus who expressed the desire to conceive were often older than the average age of women conceiving in one report [12]. Furthermore, delays in planning conception in lupus patients may reflect advice that they should plan to conceive after a 6-month flare-free period at a time when their medications have been adjusted to those that are considered safe for pregnancy so that they have the greatest chance of a successful pregnancy without complications for mother or fetus [11]. But in some cases, due to age-related effects on the quality of the eggs or possibly disease-related effects (see below), the patient may no longer be able to conceive and maintain a pregnancy to term.

Disease-related causes of infertility

Female associated

Primary ovarian failure. Primary ovarian failure (POF), alternatively known as premature ovarian failure, is a condition characterized by premature amenorrhoea (at least 4 months and usually 12 months) with raised circulating (>40 mIU/l) serum follicle-stimulating hormone (FSH) on two separate occasions several months apart and low oestrogens before the age of 40 years [15–17]. In lupus patients, it is most often due to autoimmune causes or drug induced and it presents with amenorrhoea, although not all patients with amenorrhoea or menstrual disturbance have ovarian failure. Impaired ovarian reserve is associated with raised FSH levels and may be preceded by a reduction in anti-Müllerian hormone levels [18, 19]. Anti-Müllerian hormone levels appear to be a better predictor of ovarian reserve than antral follicle counts [20].

Menstrual disturbances in SLE patients. Menstrual disturbances are common among SLE patients and range from amenorrhoea to menorrhagia. The latter is most often due to anti-coagulation therapy given to those with thrombotic complications and only rarely due to thrombocytopenia. Amenorrhoea may occur, not only as a result of cyclophosphamide (CYC) treatment causing ovarian failure (see below) [21], but also as a result of the disease itself. Episodes of amenorrhoea have been associated with anti-corpus luteum antibodies and with raised FSH levels, suggestive of autoimmune, SLE-related menstrual dysfunction [21]. Pasoto et al. [22] showed that menstrual irregularity, in the absence of alkylating agents such as CYC, was prevalent in 53% of consecutive adult lupus patients under 40 years of age. Patients with high disease activity (SLEDAI > 8) were more likely to have menstrual disturbance than those with less disease activity. Interestingly, in this group of patients, there was no evidence for an association with hormonal perturbations, such as in the hypothalamic–pituitary axis, that could have explained such menstrual disturbance.

Similarly, female patients with juvenile SLE (<18 years of age) have been reported to suffer from amenorrhoea during periods of high disease activity [23]. These patients have normal or even low FSH levels, in contrast to those with POF in whom FSH levels are raised [18], raising the possibility that the cause of the menstrual irregularity is due to the effects of the disease on the reproductive organs rather than a derangement of the hypothalamic–pituitary axis [23]. Hashimoto’s thyroiditis can be associated with SLE and may also trigger menstrual irregularities albeit through endocrine disturbances [24].

Endometriosis is a recognized cause of infertility in women without SLE, due to the development of adhesions that obstruct the fallopian tubes or disturbance of follicular development [25]. Several reports have identified immune abnormalities in infertile patients with endometriosis including both cell-mediated and humoral autoimmunity [26]. Together, this raises the possibility of infertility associated with autoantibodies and cell-mediated immune dysfunction in lupus. Some studies have suggested an association between endometriosis and SLE [27, 28], although several other reports failed to show such an association [29, 30].

Cervico-vaginal inflammation and other infections secondary to SLE. Given that certain infections may cause infertility in the general population, and that SLE and/or immunosuppressive treatment may increase the likelihood of infection in exposed individuals [31], it may be hypothesized that patients with SLE may be more likely to become infertile by infection. Evidence is now emerging that young women with SLE are more susceptible to sexually transmitted infection than controls and that those who have a higher SLEDAI DAS are most at risk [32]. CMV and the EBV are more common in lupus patients than controls and have been implicated in infertility, but there is no specific evidence relating these infections to infertility in lupus [33–35]. More studies are needed regarding the incidence of Chlamydia trachomatis infection in SLE patients and its impact on fertility, as this is an important cause of infertility in young women in general. It is important in managing patients with lupus to identify those that may be exposed to sexually transmitted infection and to refer them for appropriate investigation and treatment before complications, including infertility, develop.

Male associated

Testis damage from SLE. Soares et al. [36] showed a significant reduction in testis volume in men with SLE as determined by US imaging, which correlated with the degree of sperm abnormalities. It was suggested that this reduction was most likely due to damage by SLE to the seminiferous tubules. In support of this belief, inhibin B
(secreted from the seminiferous tubules) concentrations are significantly reduced [37] in some patients. Furthermore, FSH and luteinizing hormone (LH) concentrations are raised in these patients presumably because of a loss of negative feedback upon the pituitary gland [38]. Several reports have described the presence of anti-sperm antibodies in patients with SLE and some have said this could explain the impairment of spermatogenesis in these patients [39]. However, such antibodies are found in healthy, fertile patients, too, and it is difficult to explain male infertility from this perspective alone.

One study identified that male patients with SLE are 14 times more likely to have Klinefelter’s syndrome than healthy controls [40]. Patients with Klinefelter’s syndrome often have low testosterone levels with high FSH and LH levels and are usually infertile. Although they can be treated with testosterone supplementation to improve their masculinity, surgical removal of sperm and in vitro fertilization (IVF) therapy may be required to restore fertility. This approach raises certain ethical dilemmas and at the very least requires genetic counselling, but has been associated with the birth of children with normal karyotype [41, 42].

Gender non-specific

Lupus nephritis. Lupus nephritis affects between 30 and 75% of patients with SLE depending on the nature of the cohort studied, particularly ethnic and racial background [43, 44]. Those patients who deteriorate and develop chronic renal failure are likely to develop infertility through hypothalamic-pituitary dysfunction. The result in males is often erectile dysfunction with reduced spermatogenesis, whereas in females, menstrual irregularity with anovulatory cycles manifest [45]. Indeed, patients who have renal failure or are on haemodialysis tend to have raised FSH and Luteinising hormone (LH) concentrations [46], which reduces the production of gonadotropin releasing hormone (GnRH) from the hypothalamus. Therefore, this provides an explanation for deranged gonadotrophic factors that could lead to infertility in patients with renal impairment due to lupus nephritis.

APS (Hughes’ syndrome). Secondary APS occurs in ~30% of SLE patients and is well recognized to cause spontaneous abortions, stillbirths and premature births [47] as well as venous and arterial thrombotic events. For many years, APS has been considered a risk factor for fetal loss, rather than a condition that can affect the ability to become pregnant [48]. However, there are increasing reports, indicating that there may be an earlier influence of APS on fertilization, implantation and even reproductive function as a whole. APS can lead to thrombosis of main vessels draining the reproductive organs [49], thereby threatening fertility. Moreover, some studies are now associating APS with POF [50] and patients presenting for assisted conception due to infertility [51]. Furthermore, aPLs against the trophoblast could impair implantation of the blastocyst and so while not affecting conception itself [52, 53] would make the patient appear infertile. In light of this, APS in women should be considered as a risk factor for infertility in women with lupus, though some cases may be related to failure of implantation rather than failure of conception.

Treatment-related causes of infertility

**CYC-induced POF**

POF may be drug induced and is associated with sustained high FSH levels [46]. CYC is a well-known gonadotoxic agent that can cause POF and has been shown to deplete healthy oocytes [54]. Its toxicity is associated with two independent risk factors: the cumulative dose of CYC [55] and the age at which the drug is administered [55–57] (Tables 1 and 2). For instance, one study showed that 37.3% of 67 patients treated with CYC developed amenorrhoea with a cumulative dose of 8.7 g (S.D. 0.6 g) (mean age: 31 years; range 17–46 years) [57]. They also highlighted how a higher damage index score was associated with an increased risk of POF, which may reflect previous high disease activity that contributed to infertility [58]. Boumpas et al. [59] showed that increasing age and dose of CYC were risk factors for POF. This finding has been supported in other studies [55–57, 60, 61]. Patients are more likely to maintain normal menstruation and fertility if they receive CYC at a younger age (<30 years), as a shorter i.v. pulse course (<6 months), lower cumulative dose (<7 g dose) [57, 62] and in the absence of amenorrhoea before, or during, the CYC treatment [56].

The St Thomas’ or Euro-Lupus protocol (six fortnightly doses of 500 mg CYC) has been associated with a lower incidence of POF when contrasted with the larger dose.

**Table 1** Percentage chance of developing POF according to individual’s age and dosage

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient age group, years</th>
<th>Number of pulses, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boumpas et al. [59]</td>
<td>≤ 7</td>
<td>0 (n = 4)</td>
</tr>
<tr>
<td>(n = 39)</td>
<td>≥ 15</td>
<td>17 (n = 12)</td>
</tr>
<tr>
<td>26–30</td>
<td>12 (n = 12)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>25 (n = 4)</td>
<td></td>
</tr>
<tr>
<td>100 (n = 4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table was modified from Boumpas et al. [59] with permission from the Annals of Internal Medicine.

**Table 2** Percentage chance of developing POF according to individual’s age and dosage

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient age group, years</th>
<th>Dosage used, gm²</th>
<th>Percentage affected with POF, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ioannidis et al. [61]</td>
<td>&lt; 25</td>
<td>-</td>
<td>11</td>
</tr>
<tr>
<td>(n = 67)</td>
<td>≥ 32</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>≥ 32</td>
<td>12</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Ioannidis et al. [61].
less-frequent National Institutes of Health (NIH) regimen (6
monthly pulses followed by either 3 monthly pulses for
2 years or 3 monthly continued for 1 year after remission
is achieved in patients with lupus nephritis) [63–66]. This
is consistent with previous data suggesting that lower abso-
luate and cumulative doses of CYC are associated with
less risk of infertility. Route of administration of CYC
does not influence the risk of POF [55, 67].

Following cessation of CYC, many patients exhibit
normal menstruation and can conceive without the fetus
showing any congenital anomaly. This is despite the many
concerns raised from animal studies identifying an
increased risk of mutations with CYC [68]. It is recom-
mented that plans to conceive are delayed, until at least
3 months after the last dose, to avoid the risk of terato-
genicity. MMF is becoming recognized as a suitable alter-
native for CYC in the induction and maintenance therapy
for lupus nephritis [69, 70], and is often favoured as it does
not cause POF, although it is teratogenic [71].

**Impaired spermatogenesis in males**

Given that CYC destroys dividing cells, spermatogenesis is
impaired during treatment. Sperm quantity and quality
have been shown to be significantly impaired in boys trea-
ted with post-pubertal CYC therapy compared with con-
trols [36]. CYC is associated with reduced Leydig cell
and with reduced levels of testosterone after treat-
ment with CYC [72]. Methotrexate (MTX) and sulfasalazine
(SSZ), which may be used in the treatment of SLE, can also
reduce sperm count and may cause infertility in males.

**Non-steroidal anti-inflammatories**

The use of NSAIDs in women with lupus has the capacity
to increase the risk of infertility by inducing luteinized
unruptured follicle syndrome [73–75]. This is defined as
the failure of a follicle to rupture between Days 10 and
20 of the menstrual cycle as visualized by US [76].
However, the risk associated with NSAIDs is contentious.
While prostaglandins are involved in ovulation, other me-
diators including hormones participate also, and may be
altered in lupus patients. At present, given the lack of
rigorous epidemiological data, current data come from
uncontrolled case series and animal studies that describe
this phenomenon [75–77]. Women having problems con-
ceiving should be advised to stop NSAIDs, but not all
women on NSAIDs who wish to become pregnant have
to stop them on the basis of present evidence [71].

**CSs**

Menstrual irregularities have been attributed to high-dose
CSs administered to SLE patients [78] and menstrual dis-
turbances have been described in patients with Cushing’s
syndrome. However, it can be difficult to disentangle ir-
gularities in menstrual cycle resulting from the effects
of active disease on the hormone profile from those due to
therapy used to treat active lupus.

**MTX**

MTX is well documented to cause teratogenicity, espe-
cially in the common doses used in SLE; in higher
doses, it induces abortion. The risk of infertility after
MTX use appears very small [79].

**Psycho-social aspects influencing fertility**

Infertility, or apparent infertility, may cause significant
stress in the relationship of lupus patients with their part-
ner, due to effects on their own self-esteem and mental
well-being [80]. SLE itself can cause disorders of affect,
notably depression, fatigue and loss of libido/sexual func-
tion in women [81, 82]. Likewise, sexual dysfunction, such
as reduced libido and impotence, can be present in men
[77, 83]. Moreover, drugs used in the treatment of SLE
may diminish libido further, notably CSs [77], although
the effects of active disease may be hard to distinguish.
These psychological factors may be responsible for a
higher probability of apparent infertility through reduction
in the frequency of intercourse [10], thereby decreasing
fecundity. The effect of patients’ interpersonal relation-
ships with their respective partner may limit family size
when compared with controls [10] and so when consider-
ing the causes and treatment of infertility, both the organic
and the psychosocial effects that SLE can have on fertility
should be considered.

**Treatment strategies to promote and safeguard fertili-
yty**

**General principles**

When patients are prescribed CYC for severe lupus activ-
ity, it should be at the lowest effective dose possible and
for the shortest duration, particularly in older women. In
some instances, it may be possible to use a different
disease-modifying and steroid-sparing therapy, such as
MMF [84]. Counselling should be provided to give approp-
riate information, alleviate any anxiety regarding infertility
and to encourage patients towards their therapeutic goals
[77]. When CYC is deemed necessary to prevent renal
failure, which itself can cause infertility or problems main-
taining a successful pregnancy to term, gonadal protec-
tion may be considered in those considered at risk of
therapy-induced POF.

**Prevention of POF**

Gonadotrophic receptor hormone agonist leuprolide. A
gonadotrophic receptor hormone agonist, leuprolide, has
been shown to be protective against POF when adminis-
tered 10–14 days before each CYC pulse. In so doing,
leuprolide causes a drastic reduction in oestrogen and
progesterone levels. Use of these analogues has been
demonstrated to significantly reduce the risk of POF in
patients with SLE from 30 to 5% [85].

**Oocyte storage.** Given that there are only a finite number
of oocytes, cryopreservation of gametes in women before
gonadotoxic treatment could provide a means of conceiv-
ing after follicle depletion with CYC [86]. One danger of
obtaining oocytes is that the hormonal manipulation
required may trigger an exacerbation of SLE as a result
of raised oestrogen levels following ovarian stimulation.
While the risk of the oestrogens on disease activity is
controversial [87], it is probable that many physicians will be reluctant to recommend this procedure, especially in patients with unstable disease due to the delay involved in established definitive cytotoxic therapy in someone with severe disease (as CYC would not have been considered otherwise). It should also be noted that there is an increased risk of thrombosis associated with exogenous oestrogen therapy [12, 88]. The topic of oocyte cryopreservation has been eloquently reviewed by Tao et al. [89].

IVF. While IVF can be achieved without ovarian stimulation or using clomiphene, the yield of oocytes is low. However, ovarian stimulation using GnRH agonists provides a controlled means of obtaining healthy oocytes that can be retrieved 24–36 h post-GnRH administration. Such approaches also increase serum levels of oestrogens and increase the risk of thrombosis and possibly flare, although the lupus flare rate is relatively low. Thrombosis often occurs in the context of overt ovarian hyperstimulation syndrome (OHSS), particularly with more aggressive ovarian stimulation regimens, which should be avoided in lupus patients especially if they have APS or antibodies. A detailed discussion of these issues is beyond the scope of this review, but an excellent review has recently been published [90]. Once the oocytes are collected, they can be fertilized using intra-cytoplasmic sperm injection. The embryo can then be injected intra-uterine at the two- or four-cell stage [91].

The most threatening conditions in affected women undergoing ovarian stimulation are lupus flares and thrombosis, with the latter being especially associated with the occurrence of an overt OHSS. Friendly ovarian stimulation, single embryo transfer, avoidance of OHSS, administration of co-adjuvant therapy and use of natural E(2) or P through a non-oral route may constitute the safest approach. Systemic lupus manifested in acute flares, badly controlled arterial hypertension, pulmonary hypertension, advanced renal disease, severe valvulopathy or heart disease and major previous thrombotic events are situations in which to discourage assisted reproductive technologies, especially due to the high risk of complications for both mother and fetus during pregnancy and puerperium [90].

Testosterone. The role of testosterone in males is to maintain spermatogenesis [92]. Testosterone administered 100 mg i.m. fortnightly has been shown in a randomized control trial to preserve fertility while on CYC [93]. The rationale for this approach was that by administering testosterone and thereby reducing endogenous gonadotrophin release, one could render the germinal epithelium less active with fewer cellular divisions, and thus limit the effects of CYC damage on dividing cells.

Conclusion

Although many authors state that the prevalence of infertility in SLE patients is no greater than the average population rate, there does appear to be a significant risk of SLE and its treatment causing infertility. While many patients with lupus develop the disease after they have had one or more children, there is a significant proportion of patients (especially non-Caucasian lupus patients) who develop the disease before they have had any children or completed their families. Moreover, although it is widely recognized that CYC can cause menstrual irregularity, amenorrhoea, impaired spermatogenesis and infertility by inducing ovarian/testicular failure, it is less well recognized that the disease itself can reduce fertility through autoimmune mechanisms, hormonal disturbances or renal failure. Optimal management of patients in the reproductive age group, both females and males, requires physicians caring for lupus patients to consider how best to reduce the risk from all of these factors predisposing to infertility. Best practice will vary with the age of the patient and the nature of lupus disease activity. Plans for pregnancy in the future in lupus patients will need careful discussion. Physicians should ensure that patients understand that there are risks for infertility associated with the disease and/or its therapy in both females and males and the difference between possible infertility and teratogenesis associated with the administration of certain drugs such as CYC and MTX.

Rheumatology key message

- The causes of infertility in SLE are wide ranging, but often preventable and treatable.

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References


