Treating infertility in autoimmune patients

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Fertility in patients with SLE and other systemic autoimmune disease is usually unaltered. However, fertility may be impaired by anovulation during episodes of active disease or chronic renal failure, administration of NSAIDs, high dose of corticosteroids and cyclophosphamide. Early pregnancy loss occurs in SLE patients with aPLs. An association of autoimmune disease with infertility has been suggested, but the studies are not conclusive. Ovulation stimulation as a fertility treatment could theoretically induce SLE. However, two recent studies did not find previous use of fertility drugs and in vitro fertilization to be more frequent in the history of SLE patients when compared with controls. Patients with SLE or primary APS, who are undergoing infertility treatment, could be at risk of flare or thrombosis. In the past 10 yrs, many reports have been published regarding the risk of lupus exacerbation associated with controlled ovarian hyperstimulation; not all found excess risk. At the moment we do not have any prospective study in this field. A trend towards a worse prognosis in cases of SLE patients undergoing assisted reproductive techniques (ARTs) for pregnancy rate, live-birth rate and maternal complications can be seen. If hormonal ovarian stimulation is useful, well-advised management would authorize a low effective gonadotropin dose in a patient whose disease has been silent preferably for at least 6 months. Further data are needed to establish safety and efficacy of ART in SLE patients.

In Western countries, the rate of infertility is about 10–20% and is age dependent. Since the fertile partner among couples can be either the man or the woman, specification of which sex contributes to infertility is necessary in studies of patients with autoimmune diseases.

This review focuses on patients with SLE—the only group for which extensive data are available. The review asks the following questions: (i) do autoimmune diseases or their treatments cause infertility? (ii) Does infertility treatment worsen autoimmune diseases? (iii) Do autoimmune diseases worsen the results of treatment of infertility? (iv) Are there special rules for infertility treatment for autoimmune patients?

In European and North American population, the prevalence of SLE is 15–50 cases per 100,000 subjects, with an incidence of 2–8/100,000/yr. Figures for black Americans are three to four times higher, and for all populations are highest in women 13- to 55-yrs old. SLE mainly affects women of reproductive age (prevalence in white, 1/1000 and in black, 4/1000). In patients with SLE and other systemic autoimmune diseases, infertility most often has a specific attribution: anovulation during episodes of active disease or chronic renal failure. NSAIDs may lead to unruptured follicle syndrome [1]. High doses of corticosteroid treatment as well as cyclophosphamide affect ovulation and gametes. Pregnancy loss occurs in SLE patients with aPLs.

Evidence that autoimmune disease is associated with infertility is based on an increased SLE prevalence (1.5% or 2 women) found in a cohort of 140 infertile women, higher than in fertile women [2]. The small sample size, however, makes the study inconclusive. Even less convincing, in the two cases in this study, in which the women had SLE, one couple had male infertility and the cause for the second couple was unexplained infertility.

An association between autoimmune disease and endometriosis has been suggested. Theoretically, defective clearance of apoptotic endometrial cells in a pro-inflammatory environment in endometriosis could trigger autoantibody production, particularly in a genetically predisposed subgroup that develops autoimmune diseases [3]. A USA 1998 survey in women with endometriosis vs the matched control group who did not receive a GnRH agonist found previous use of fertility drugs and fertilization to be more frequent in the history of SLE patients when compared with controls.

Infertility occurs as a consequence of some autoimmune disease treatments and of SLE, in particular. Cyclophosphamide impairs fertility by damaging ovarian follicles, impairing follicular maturation and/or depleting primordial follicles. Temporary amenorrhea will result when maturing follicles are destroyed. Permanent amenorrhea or premature ovarian failure (POF) will result when all primordial follicles are destroyed. Cyclophosphamide-induced amenorrhea is dose- and age dependent. Females have 6–7 million oocytes at fetal week 20, 1–2 million oocytes at birth, 25 000 at the age of 37 yrs and 1000 at the age of 51 yrs [5]. The physiological loss of fertility—normally occurring at 7 yrs before menopause—depends on both quality and quantity of oocytes. The cumulative dose of the cytotoxic drug is a key factor. The total dose of cyclophosphamide needed to induce amenorrhea is 20 400 mg at the age of 20 yrs, 9300 mg at the age of 30 yrs and 5200 mg at the age of 40 yrs [6].

Nowadays most therapeutic protocols for lupus nephritis limit the cyclophosphamide dose, mainly administered by intravenous injection, based on two main schedules: 1-g bolus/month for a total of six bolus, followed by 3-month maintenance boluses for 6 months or 500-mg bolus/week, for a maximum of six to eight boluses (according to therapy response). Oral administration (1–2 mg/kg/day) is less often used today. Amenorrhea is rare if the cumulative dose is between 3.5 and 7 g in females under 25 yrs of age; it occurs in 12% of 26- to 30-yr-old patients and 25% of patients older than 30 yrs [7].

A high follicle-stimulating hormone (FSH) level is found in 39% of patients treated with cyclophosphamide under 30 yrs and in 59% of patients between 30 and 40 yrs, implying a future reduction of fertility [8]. Even a minimum dosage of alkylating drug produces follicular damage. Some authors argue that use of gonadotropin-releasing hormone (GnRH) agonists during cyclophosphamide treatment protects fertility as compared with the matched control group who did not receive a GnRH agonist [9].

Mechanisms through which GnRH agonists may decrease chemotherapy-associated gonadotoxicity include [10]: GnRH agonist blocking the receptor, decreased gonadotropin concentration, decreased ovarian perfusion due to low oestrogen, a sphingosine-1-phosphate-mediated event or germ-line stem cell preservation. Data supporting the protective effect of GnRH

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agonists are controversial [11] and are based only on observational studies on patients with neoplasia.

Fertility can also be damaged without occurrence of amenorrhoea. It is controversial whether early menopause should be assumed to be a toxicity indicator, since patients continuing to menstruate could exhaust ovarian function earlier than non-affected women of the same age [12]. Although hypogonadism produces a situation similar to pre-puberty, which might be protective of fertility, a wide prospective study showed the risk of POF in females who as infants had undergone chemotherapy is 13 times higher than normal [13]. Even the administration of GnRH agonists in patients with SLE is controversial, since GnRH agonists worsened SLE in a murine model [14]. GnRH analogues also induce irreversible bone density loss.

Some authors believe that sex hormones play an important role as modulators of the autoimmune disease onset/perpetuation since oestrogens enhance humoral immunity [15]. Thus, ovulation stimulation as a fertility treatment could theoretically induce SLE. However, two recent studies did not find previous use of fertility drugs and in vitro fertilization to be more frequent in the history of SLE patients when compared with controls [16, 17].

In patients with the disease, hormonal treatments for ovulation induction should start when the illness is silent, preferably for at least 6 months, and should exclude patients with renal, cardiac, neurological pathology or with non-controlled arterial hypertension. A new disease flare can however take place, although rarely [18]. Since infertility treatment usually requires hormonal manipulation, SLE or primary APS patients could be at risk. In the past 10 yrs, many reports discuss the risk of lupus exacerbation, including fatal cases, associated with controlled ovarian hyperstimulation and high oestrogen levels [19-27]; not all found excess risk. No prospective study is available in this field.

Induction of ovulation is performed with clomiphene or gonadotropins, used in different doses, depending on the following indications: (i) for treatment of anovulation or empirical treatment of unexplained infertility (aiming at obtaining single-follicle ovulation)—clomiphene or gonadotropins in low doses (50–100mg clomiphene for 5 days or 50–100 U/day of urinary or recombinant gonadotropins); (ii) for intrauterine insemination (two or three follicles needed)—clomiphene or gonadotropins in low/medium doses (100mg clomiphene or 75–150 U of urinary or recombinant gonadotropins); (iii) for in vitro fertilization with embryo transfer (IVF-ET) with or without intra-cytoplasmic sperm injection, requiring controlled ovarian hyperstimulation, since a large number of follicles is needed with gonadotropins in high doses (100–450 U/day).

Overall, all anovulatory patients and at least 40% of infertile normo-ovulatory patients undergo the second or third of the above procedures, called assisted reproductive techniques (ARTs).

During ovarian stimulation for IVF-ET oestradiol levels reach 6-fold physiological values and luteal phase progesterone levels are 3-fold the normal levels. In comparison, during normal pregnancy the maximum level of oestradiol is 6- to 8-fold the non-pregnant level, but the total oestrogen levels at term are 100-fold the non-pregnant values. Oestrogen daily production at term equals to the amount produced by 1000 ovulatory women each day; in the course of a pregnancy the amount of oestrogens produced is comparable with the oestrogen secreted by 150 women during a whole year. During pregnancy progesterone levels are 10- to 20-fold the values of normal luteal phase [28, 29].

However, an IVF-ET cycle is more complex than implied by hormone levels. Before echo-guided retrieval, oocytes undergo a final meiotic maturation for which a dose of human chorionic gonadotropin (hCG) is administered 34–36 h in advance, producing an early activation of the coagulation cascade and a later activation of fibrinolysis [30]. The hCG also induces an increase in VEGF [31]. Changes in VEGF levels and coagulation factors are particularly remarkable in cases of ovarian hyperstimulation syndrome (OHSS), the most serious and potentially fatal iatrogenic event due to ART. Severe OHSS occurs in 1% of the patients after multiple ovulation induction and mild–moderate OHSS in 4–10%.

The cardinal event of this syndrome, known since 1943, is a third space fluid shift related to the ovarian enlargement with production of substances that increase vascular permeability causing ascites, pleural effusions, haemoconcentration, reduced renal perfusion, disseminated intravascular coagulation, adult respiratory distress syndrome and thromboses, with a mortality rate between 1/45000 and 1/500000.

Recent observations from animal studies suggest that the VEGF plays a pivotal role in increasing vascular permeability in hyperstimulated subjects [32]. In autoimmune diseases, the VEGF level correlates with disease activity and falls during pharmacological treatment. Not surprisingly, some cardiac features of the OHSS can also be considered as lupus flares: pleural or pericardial effusion, oliguria, anuria, respiratory distress, low creatinine clearance and thrombo-embolism [prevalence of venous thrombo-embolism (VTE) is 1/128 in severe OHSS]. A 1997 literature review reported 54 cases of thrombo-embolic disease associated with ovarian stimulation and IVF, 75% venous and 25% arterial. Seventy-two percent of patients obtained pregnancy. Sixty-six percent of thrombo-emboli were associated with OHSS, 60% were located in the upper part of the body and 4–12% were associated with pulmonary emboli. Overall, VTE frequency is very low in IVF cycles (1.6/100 000 cycles), but OHSS increases the risk [33].

Although one might expect an increase in lupus flares during ovarian stimulation for ART, two studies on lupus flares in ART patients argue that this does not occur. Le Thi Huong et al. [27] report on 114 cycles of ovulation induction for ART in 21 women. In 13 patients, the disease was already known: SLE (6 patients), primary APS (3 patients), APS associated with SLE (3 patients) and discoid lupus (1 patient). A complication (fetal loss, SLE flare, thrombophlebitis) revealed the underlying disease in eight women: SLE (3 patients), primary APS (5 patients). An SLE flare-up appeared after 13 out of 62 (25%) cycles in SLE patients, with a rate after gonadotropins (27% per cycle) higher than that after clomiphene (6%), and, similarly, with a rate after an unplanned procedure (30%) higher than that after a planned procedure (10%). The subgroup in which the disease was known included three flares in 29 cycles and two patients out of eight had at least one flare with no cases of thrombophlebitis. Two non-SLE women who developed thrombophlebitis after gonadotropin were found to have previously unknown APS. Many patients underwent an unplanned IVF-ET. The authors do not explain this unusual feature; presumably such patients had an unpredictably high response to ovarian stimulation, which led clinicians to shift them from intrauterine insemination to IVF. Excessive ovarian response is more common in patients treated with gonadotropins than in clomiphene-treated subjects. Such a higher response could perhaps explain the higher incidence of flares registered within this group.

In the retrospective study by Guballa et al. [24], 19 patients with SLE, primary APS or high titre aPL underwent 68 cycles of ovulation induction for IVF. Out of seven patients with SLE, three had a mild lupus flare. Two patients with lupus nephritis developed OHSS and in one case creatinine levels had not yet returned to baseline values after 1 yr. Maternal complications during pregnancy were: pre-eclampsia, lupus flare in 4/19 SLE patients (20%), gastrointestinal haemorrhage due to Mallory–Weiss syndrome and diabetes. No thrombosis occurred. Post-partum complications included nephritis flare, costochondritis and suicidal depression. No conclusion can be drawn on such data, except for an increased thrombotic risk in patients with aPLs.

Successful IVF-ET indicators are: clinical pregnancy rate, embryo/fetal loss and live-birth rate for initiated cycle or for embryo transfer. In the two previously mentioned series,
results seem lower than those published in Europe in the same years [34]. In 114 cycles of IVF-ET in 21 women with SLE and/or APS [27], 18 pregnancies were obtained with a clinical pregnancy rate of 15% per cycle: 11 pregnancies after unplanned IVF and 7 pregnancies after planned IVF. Such pregnancies generated nine live births, four fetal deaths, and five embryonic losses. Pregnancy rate was similar after IVF-ET, whether the protocol was planned or not. However, three of four pregnancies after unplanned IVF-ET led to abortions, whereas six out of seven pregnancies after planned IVF-ET led to live births.

In the other series [24], 68 ART stimulations resulted in 22 pregnancies, but only 12 lasted for at least 20 weeks. Live-born children were 17: 5 of 16 cycles (31%) in 7 SLE patients, 5 of 48 cycles (10%) in 10 primary APS patients and 0 of 5 cycles in 2 women with aPL (without SLE or primary APS) resulted in liveborn children, including multiple gestations (3 twin sets with 4 surviving infants and 2 triplet sets with 3 surviving infants). In conclusion 14 liveborn children were obtained. Seven of 14 living children (50%) were premature (all from SLE patients); three had neonatal lupus and one had pulmonal stenosis. Five surviving infants (38%) had complications unrelated to prematurity.

Such data are very limited and much clinical information on treated patients is lacking. A trend towards a worse prognosis in cases of SLE patients undergoing ART both for pregnancy rate and live-birth rate can be seen.

While obstetrical complications in SLE and aPL patients are known, it is less clear whether SLE and APS decrease pregnancy rate. Should such a trend be demonstrated true, one could argue that the problem is due to the systemic illness itself or to circulating antibody. Some studies report an increased prevalence of aPL among women undergoing repeated unsuccessful IVF-ET, but prospective studies examining the aPL ON IVF-ET outcomes demonstrate that such antibodies do not significantly affect either the implantation or ongoing pregnancy rates [35]. Hornstein et al. [36] reached the same conclusions.

A recent prospective study deals with the effect of ANAs on IVF-ET success rate. A retrospective analysis on 45 treatment cycles in 25 patients with ANA (titre 1:40) and 80 cycles of 63 negative patients. Embryo implantation rates were 14% in positive patients and 32.4% in negative patients, whereas pregnancy rates were of 28% in positive patients against 54% in negative patients. Outcomes tend to overlap within three cycles, if patients undergo repeated treatments.

A first objection to this study deals with the title threshold value set at 1:40, a low value, leading to a high incidence of 28.7% ANA-positive patients. A pregnancy rate of 54% at first cycle in ANA-negative patients is much higher than the rate generally reported by international registries. Furthermore, pregnancy rate referring to repeated cycles remains constant or slightly decreases during the first three to four attempts [37], whereas in this study the pregnancy rate in ANA-positive patients increases at any further attempt, with no therapeutic intervention. The phenomenon observed by the authors seems to be not the conclusion of a spontaneous and unexplained failure of implantation, but instead a regression towards the mean, a rather common event in statistics, occurring when repeated measurements are used [38].

New protocols for the stimulation of multiple ovolutions with limited use of gonadotropins have been recently set, aiming at reducing OHSS risks, multiple pregnancies, economic burdens and the couple’s emotional stress and keeping a good oocyte quality as well as similar success possibilities. This concerns all patients, but mainly those who must avoid or limit their exposure to high oestrogen levels, for instance, patients suffering from autoimmune diseases or previous oestrogen-dependent neoplasia.

Intruterine insemination treatments do not necessarily require ovulation induction; guidelines show that insemination efficacy is granted without gonadotropins, reducing the risk of multiple pregnancies [39-41]. As an alternative to conventional protocols that use a high gonadotropin dosage to maximize the number of retrieved oocytes, new stimulation protocols have been proposed for IVF-ET. Alternative protocols, commonly known as ‘friendly’, include [42]: (i) natural IVF cycle—no stimulation, collection of a single oocyte; (ii) modified natural IVF cycle—administration of GnRH antagonist, addition of low-dose FSH or hMG (human Menopausal Gonadotropin) and hCG to collect a single oocyte [43]; and (iii) mild IVF—administration of GnRH antagonist, fixed low gonadotropin dose 150 IU/day, late beginning of administration during the cycle and hCG to collect 2–7 oocytes [44, 45]. Patients with an absolute contraindication to gonadotropins can be treated with anti-oestrogens or aromatase inhibitors (tamoxifen or letrozole) [46].

Such protocols cause a lower number of yielded oocytes and transferred embryos, although per cycle and cumulative results are satisfying. A low oocyte yield in the current controlled ovarian hyperstimulation protocol identifies poor responder patients, and good responses need a high number of retrieved oocytes. A low oocyte yield in mild stimulation protocol is the expected response, the environment in which follicle dominance is established being more physiological, increasing the probability for the single oocyte to obtain a pregnancy. A mild stimulation applied later in the cycle takes advantage of the physiological rise of FSH that occurs in the early days of the cycle. In this protocol, it is not necessary to support the initial recruitment of follicular maturation with exogenous gonadotropins, allowing for a reduction in drug expenses and a physiological selection of the follicular dominance. In the following days, exogenous gonadotropin stimulation prevents the monofollicular dominance, with a limited number of co-dominant follicles to progress to final maturation. This approach is effective in IVF since quality–quantity relationship of retrieved oocytes also depends on the applied stimulation regimen (quality does not mean quantity). The percentage of chromosomally competent embryos assessed by pre-implantation genetic screening (PGS) is significantly higher within mild stimulation protocols [47]. With any of these protocols the patient’s oestrogen level is lower than the conventional stimulation.

Conclusion

Some patients with SLE need hormonal treatment for the couple’s infertility. If hormonal ovarian stimulation is useful, well-advised management would administer a low effective gonadotropin dose, since multiple pregnancies and OHSS can be dangerous for SLE patients. Patients with APS, a prior thrombosis, who are older than 40 yrs or who have a known thrombophilia and those who develop OHSS need thromboprophylaxis. Thromboprophylaxis should be suspended 24h before and reinstituted 24 h after the oocyte retrieval to reduce the risk of haemorrhage and should be extended if a pregnancy begins.

Further data are needed to establish safety and efficacy of ART in SLE patients. Multicentre prospective studies could give the answer in the future.

Rheumatology key messages

- Assisted reproductive techniques are feasible in some SLE patients.
- Prospective studies are needed to establish safety and efficacy of ART in SLE patients.
- The lowest effective ovarian stimulation must be used.

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