In Vitro Fertilization in 37 Women with Systemic Lupus Erythematosus or Antiphospholipid Syndrome: A Series of 97 Procedures

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ABSTRACT. ***Objective.*** To compile and assess data about complication and success rates for *in vitro* fertilization (IVF) of women with systemic lupus erythematosus (SLE) and/or antiphospholipid syndrome (APS). To date, such data are sparse.

Methods. This retrospective study described women with SLE and/or APS who have had at least 1 IVF cycle.

Results. Thirty-seven women with SLE (n = 23, including 8 with antiphospholipid antibodies), SLE with APS (n = 4), or primary APS (n = 10) underwent 97 IVF procedures. For 43% of cases, the infertility was female in origin, for 19% male, 14% mixed, and 24% unexplained. No women had premature ovarian insufficiency because of cyclophosphamide. Median age at IVF was 34 years (range 26–46). The median number of IVF cycles was 2.6 (1–8). Patients were treated with hydroxychloroquine (72%), steroids (70%), azathioprine (3%), aspirin (92%), and/or low molecular weight heparin (62%). There were 27 (28%) pregnancies, 23 live births among 26 neonates (3 twin pregnancies), 2 miscarriages, and 2 terminations for trisomy 13 and 21. Six spontaneous pregnancies occurred during the followup. Finally, 26 women (70%) delivered at least 1 healthy child. Complications occurred in or after 8 IVF cycles (8%): SLE flares in 4 (polyarthritis in 3 and lupus enteritis in 1) and thromboembolic events in 4 others. One SLE flare was the first sign of previously undiagnosed SLE. Poor treatment adherence was obvious in 2 other flares and 2 thromboses. No ovarian hyperstimulation syndrome was reported.

Conclusion. These preliminary results confirm that IVF can be safely and successfully performed in women with SLE and/or APS. (First Release January 15 2017; J Rheumatol 2017;44:613–18; doi:10.3899/jrheum.160462)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS ANTIPHOSPHOLIPID SYNDROME INFERTILITY
IN VITRO FERTILIZATION ASSISTED REPRODUCTIVE TECHNOLOGY PREGNANCY

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Accepted for publication November 25, 2016.

Systemic lupus erythematosus (SLE) mainly affects women of childbearing age and female hormones are involved in its pathogenesis[1,2]. Spontaneous pregnancies in women with SLE and/or antiphospholipid syndrome (APS) carry a potential risk of SLE flares, thrombosis, and obstetric complications[3].

The fertility of these patients is usually considered normal except for those treated with high doses of cyclophosphamide (CYC). Nevertheless, infertility occurs among women with SLE as it does among women in the general population[4,5]. These patients with SLE may then require *in vitro* fertilization (IVF) to conceive, which may, because it requires hormonal manipulation, increase the risk of SLE flares and thromboses[6,7,8]. Because this situation remains infrequent, few studies have specifically examined the risk: only 2 series (1 including 17 women with SLE and/or APS who had IVF[6], and the other 10 patients[9]), together with several case reports[7,8,10,11]. Note that the numbers reported for these series do not count the women in these studies with ovulation induction only and no IVF.

We report our experience with 37 women with SLE and/or APS who underwent 97 IVF procedures. The aim of our study was to assess the risk of complications and the success rate.

MATERIALS AND METHODS

Patients. Our retrospective study took place in 4 internal medicine centers in France (Cochin and Pitié-Salpêtrière in Paris, Nantes, and Reims). Inclusion criteria were (1) a diagnosis of SLE according to the American College of Rheumatology criteria[12] and/or APS according to the Sydney criteria[13], and (2) at least 1 IVF procedure between 1995 and 2014 (with 91 procedures performed since 2000). IVF procedures were supervised by an internist with a prepregnancy counseling and a followup during IVF and pregnancy to control SLE activity.

Approval was not required in accordance with the policy of our institution.

Variables. Variables examined were age, obstetric history, etiology of infertility, previous manifestations of SLE and APS, disease activity, treatments for SLE and APS (past and current, including CYC exposure), whether an internist monitored the IVF cycle, protocols of ovarian stimulation (agonist or antagonist), complications during and after IVF (with a special focus on SLE flares and thrombosis), ovarian hyperstimulation syndrome (OHSS), and success of IVF (defined by the occurrence of a pregnancy).

We considered that IVF was appropriate for women without any severe SLE flares (renal or neurological) for 1 year or any moderate flares for 6 months and in the absence of severe damage such as renal insufficiency, uncontrolled systemic hypertension (HTN), or pulmonary HTN.

Definitions. An IVF procedure was defined as either the induction of ovulation and oocyte retrieval (although the embryo transfers could be done during the same cycle or be frozen to be used later) or an IVF procedure using a donated oocyte with an estrogen and progesterone preparation. Aspirin was usually stopped 7 days before oocyte retrieval and resumed the next day in patients treated with aspirin or after embryo transfer in those treated with anticoagulants.

An SLE flare was defined by an increase of at least 3 in the SLE Disease Activity Index score[14]. Miscarriage was defined as a spontaneous pregnancy loss before 10 weeks of gestation (WG), and fetal death as a pregnancy loss at or after 10 WG. Preeclampsia was defined by HTN (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and proteinuria as ≥ 0.3 g/24 h. Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome was defined by the simultaneous presence of those 3 levels (< 150,000/mm^3, aspartate aminotransferase or alanine aminotransferase > 40 IU/l). Preterm birth was defined by a live birth before 37 WG.

Statistical analysis. For the descriptive analyses, quantitative variables are expressed as means and SD, and qualitative variables as numbers and percentages. The chi-square test was used to compare the qualitative variables. The threshold of statistical significance was set at 0.05.

RESULTS

Patients. The study included 37 women. They had SLE alone (n = 15, including 1 case of SLE diagnosed during the IVF procedure), SLE associated with antiphospholipid antibodies (aPL; n = 8), SLE associated with APS (n = 4), and primary APS (n = 10). Median age at diagnosis was 27 years (range 13–41) for SLE and 30 years (13–40) for APS. Mani-festations among the 27 women with SLE were articular (n = 22), cutaneous (n = 19), hematological (n = 9), cardiac (n = 5), renal (n = 4), pulmonary (n = 2), and neurological (n = 1). None had chronic renal insufficiency. Among the 14 women with APS, clinical manifestations included obstetric complications (n = 8) and/or venous (n = 5) and arterial thromboses (n = 2). The aPL were anticardiolipin antibodies (n = 11), anti-β2-glycoprotein I antibodies (n = 7), and/or lupus anticoagulant (n = 5).

Twenty women had never been pregnant (54%), and 33 were nulliparous (89%). Ten women had had miscarriages in the past and 5 had stillbirths. Underlying causes of infertility were of female origin in 16 cases (43%: 8 endometriosis, 4 ovulation disorders, 3 ovarian insufficiency, 2 tubal anomalies, and 1 polycystic ovarian syndrome; 2 women had 2 causes of infertility), of male origin in 7 (19%), mixed in 5 (14%: 3 ovulation disorders, 1 ovarian insufficiency, and 1 endometriosis associated with male infertility), or unknown in 9 (24%). Only 1 patient had been exposed to CYC, and she did not have premature ovarian insufficiency.

IVF procedure. These 37 women underwent 97 IVF procedures (median per patient: 2.6, range 1–8). The median age at IVF was 34 years (26–46).

For 63 of the 65 IVF procedures in women with SLE (97%), the woman had had no moderate flares for at least 6 months and no severe flares for a year. None of the women with APS had had a thrombosis in the year before IVF. In all, 93 of the IVF cycles (96%) were appropriate and supervised by an internist. One IVF was performed in a patient with then undiagnosed SLE: the diagnosis was made a few days after the procedure. Only 3 IVF cycles were supervised by a gynecologist alone (women with obstetric APS with miscarriages).

Treatments of SLE and/or APS included hydroxychloroquine (HCQ; n = 70, 72%), steroids (n = 68, 70%), azathio-

prine (n = 3, 3%), aspirin (n = 89, 92%), and/or low molecular weight heparin (LMWH; n = 60, 62%; Table 1).

Ovulation induction protocols varied according to the center. Agonist gonadotrophin-releasing hormone (GnRH) protocols were used in 50 procedures (51.5%), antagonist GnRH protocols in 15 (15.5%), and retrieval took place during natural or substituted cycles in 24 (25%), and the precise procedure was unknown in 8 (8%). Oocyte donation was used for 15 procedures (15.5%) in 7 patients with a median age of 42 years (35–45).

Complications of IVF. Complications accompanied or followed 8 IVF procedures (8%; Table 2) with 4 SLE flares (in 3 women) and 4 thromboembolic events (also in 3 women). No OHSS occurred.

The 4 SLE flares involved polyarthritis in 3 cases and lupus enteritis in 1. One of these SLE flares (polyarthritis) was the inaugural symptom that led to the diagnosis of SLE. The 4 thromboembolic events included lumbo-ovarian thrombosis (n = 1), distal deep venous thrombosis (n = 2), and a distal pulmonary embolism (n = 1). All cycles with complications included an ovarian induction protocol that used agonist GnRH.

Four complications could possibly have been avoided because they were attributed to nonadherence to treatment. One patient with SLE stopped taking the prescribed steroids after IVF failed and developed progressive lupus enteritis during the next 3 months. Another woman with SLE had a joint flare in the context of poor adherence to HCQ treatment. Finally, 2 women completely stopped their anticoagulant treatment (LMWH, prophylactic for 1 and therapeutic for the other) after the oocyte retrieval; this led to deep venous thrombosis for one and a nonsevere pulmonary embolism for the other. It should be noted that all 4 women stopped adhering to treatment after the IVF procedure failed (i.e., when they did not become pregnant).

Thus, unavoidable complications apparently occurred in only 4 cases (4%), including the woman with her first SLE symptoms after IVF.

Results of IVF. In all, there were 27 pregnancies (28%), including 3 twin pregnancies: 23 pregnancies led to 23 live births (85% of the pregnancies, involving 26 fetuses), 2 to miscarriages, and 2 to terminations for trisomy 13 and 21. In addition, during the median followup of 7 years (range 0.67–20 yrs), 6 spontaneous pregnancies occurred in 6 women. Finally, 26 of the 37 women (70%) gave birth to at least 1 healthy child. The women's median age at the end of the followup was 44 years (28–59), and 21 were older than 45 years. The women's median age was similar between patients who had live births and patients without live births (35.5 and 34.4 yrs, respectively).

Table 1. Treatments of SLE and/or APS. Values are the number of IVF procedures.

Variables	SLE	SLE + aPL	SLE + APS	APS	Total
Patients	15	8	4	10	**37**
IVF procedures	**37**	**20**	**8**	**32**	**97**
Hydroxychloroquine	34	20	8	8	**70**
Steroids	33	16	6	13	**68**
Azathioprine	1	1	1	0	**3**
Aspirin	32	20	5	32	**89**
Prophylactic LMWH	15	8	2	25	**50**
Curative LMWH	0	0	6	4	**10**

Significant data are in bold face. SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; IVF: *in vitro* fertilization; aPL: antiphospholipid antibodies; LMWH: low molecular weight heparin.

Table 2. Risks associated with IVF in SLE and/or APS. Values are the number of IVF procedures.

Variables	SLE	SLE + aPL	SLE + APS	APS	Total
Patients	15	8	4	10	**37**
IVF procedures	**37**	**20**	**8**	**32**	**97**
SLE flare	1	0	2	0	**3**
SLE inaugural signs and first diagnosis	1	0	0	0	**1**
Thromboembolic events	0	0	2	2	**4**
OHSS	0	0	0	0	**0**
Uncomplicated IVF	35	20	4	30	**89**

Significant data are in bold face. IVF: *in vitro* fertilization; SLE: systemic lupus erythematosus; APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; OHSS: ovarian hyperstimulation syndrome.

The pregnancy rate did not differ significantly between women with APS or aPL alone (n = 15/60, 25%) and those without (n = 12/37, 32%, p = 0.63).

Complications during pregnancy. Complications during the 27 pregnancies obtained by IVF included 6 mild SLE flares (22%) and 1 deep vein thrombosis. Obstetric complications were preterm birth (n = 10, 37% including 5 preterm births before 34 WG), preeclampsia (n = 2, 7%), and HELLP syndrome (n = 4, 15%). Median birth weight was 2500 g (range 500–3760).

DISCUSSION

We report a large series of IVF in women with SLE and/or APS with relatively safe and effective results. Eight IVF cycles (8%) were complicated by 4 SLE flares and 4 by thromboembolic events; none were life-threatening. Four complications occurred in patients with poor treatment adherence after the IVF procedure failed to produce a pregnancy. Therefore, they may have been preventable. The other 4 were unavoidable: 2 moderate SLE flares, including the 1 in a patient with SLE first diagnosed after the IVF procedure, and 2 venous thromboses. When assessing this low complication rate, it is important to keep in mind that almost all the women in our series were in clinical remission when ovarian stimulation began and that 96% of the IVF cycles were supervised and considered appropriate by an internist. Reported complications are higher in the literature. In the first published series[6], among 17 patients (7 SLE and 10 APS) with 63 cycles of IVF, all women were in remission at the beginning of IVF and 78% were considered to be receiving adequate treatment for SLE and APS. Complications included 25% of SLE flares (in 4 of the 16 cycles of women with SLE) and 3% of OHSS (2 of 63 cycles). There were no thromboses. In the second published series[9], among 10 patients with 40 cycles of IVF (7 with SLE including 2 cases diagnosed during IVF and 1 SLE associated with aPL, and 3 APS diagnosed during IVF), only 47% of the IVF procedures were planned in consultation with an internist treating the woman for SLE and/or APS. SLE flares complicated 21% of the procedures (n = 7/33 procedures in patients with SLE). There were no cases of either thrombosis or OHSS. A few case reports have described IVF complications in this setting, including transverse myelopathy with fatal pulmonary embolism[11] and SLE flares[7,11]. SLE has been reported to be induced by IVF[10,15], and some authors have hypothesized that healthy women with "silent" SLE might develop SLE following repeated and prolonged exposure to estradiol and gonadotrophin[6,10].

The risk of thrombosis related to IVF in the general population ranges between 0.08% to 0.2% and increases to 1.7% in cases of OHSS[16,17,18,19,20]. A study reported that the main risk factors for thrombosis during assisted reproduction treatment are inherited thrombophilia and advanced age[19]. That series included no cases of SLE or APS. Interestingly, in the general population, it is believed that the use of the GnRH antagonist protocol may reduce the risk of thrombosis[21,22], perhaps because OHSS is rare with this mode of ovarian stimulation. Similarly, this antagonist protocol might also reduce both hormone-associated SLE flare and thromboembolic events in patients with SLE/APS. This protocol was used in 15 procedures of our series without any complication observed. Further studies are needed to confirm its benefits. Finally, we did not observe any thrombosis of upper limbs, a classic complication of IVF.

We did not observe OHSS in our series. It occurs more frequently in cycles that use human chorionic gonadotrophin (hCG), when very high estradiol concentrations are reached, in younger, slimmer women, in those with polycystic ovarian syndrome, with good ovarian reserve, and in multiple pregnancies[23,24,25]. The absence of OHSS may also be partly explained by using GnRH antagonist stimulation in some women. This procedure reduces the risk of OHSS risk, since agonist GnRH avoid the use of exogenous hCG to trigger oocyte maturation and since embryo transfer can be delayed by freezing the oocytes retrieved or the embryos obtained for transfer during a natural or substituted cycle[17,18,21,22]. In addition, the risk of OHSS was probably limited in our series by the cancellation of hCG injections when serum estradiol levels reached 2500 pg/ml or when the number of oocytes exceeded 10, as recommended[24].

The 28% pregnancy rate after IVF in our study is close to results reported in the general population[6,26,27]. The rate of live births among the pregnancies was 85%. Overall success rates were lower in the other 2 series. In the New York study of 17 women, 33% of IVF cycles resulted in pregnancy (n = 21/63), and only 52% (n = 11/21) lasted at least to 20 WG[6]. In the French series of 10 patients, 27.5% of the IVF cycles led to pregnancy (n = 11/40), and only 64% to live births (n = 7/11; 2 miscarriages and 2 fetal deaths)[9]. In that study, 37% of births were preterm.

We observed no statistically significant relation between APS or aPL and the IVF pregnancy rate, which was 25% in women with APS or aPL and 32% in patients without (p = 0.63). It should be noted that the relation between aPL and poor outcome in assisted reproduction treatment is controversial[6,28,29,30,31,32].

The causes of infertility varied widely and had both male and female origins. Most of our patients had primary infertility with endometriosis (n = 9) or ovarian dysfunction (n = 7). Although endometriosis is more frequent in women with SLE[33], it is usually considered that primary infertility is no more common among patients with SLE/APS than in the general population[34]. Secondary infertility in SLE may result from amenorrhea accompanying severe flares, renal insufficiency-related hypofertility, and ovarian failure secondary to CYC, an alkylating agent whose gonadotoxicity depends on both dose and age[4,5,35,36,37,38]. No infertility related to this cause was observed in our study.

The main limitations of our study include the relatively small sample size explained by the rarity of IVF in patients with SLE and APS, and its retrospective design, explaining that the ovulation induction protocols were not always available. The inclusion of ovum donation cycles, which have a milder stimulation induction protocol, may be questionable. However, because ovum donation is considered an IVF procedure, we chose to include them.

The rate of SLE flares and thromboembolic events was low (8%); these were not severe and may have been explained in 50% of cases by poor adherence to treatment. The pregnancy and live-birth rates were close to what is expected in the general population (28% and 85%, respectively). These results confirm that IVF can be safely and successfully performed in women with SLE and/or APS who are in remission and receiving adequate treatment[34,39,40]. Close monitoring is essential, especially when the IVF procedure fails, to encourage women to continue treatment adherence[41].

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