Objective: To review the current evidence regarding the relationship between systemic lupus erythematosus (SLE) and antiphospholipid syndrome and female infertility, as well as the risks associated with ovarian stimulation for ovulation induction and IVF. To establish, based on this information, guidelines for safe and successful assisted reproductive technology (ART).

Design: A MEDLINE computer search was performed to identify relevant articles.

Result(s): Systemic lupus erythematosus and antiphospholipid syndrome are not related to infertility, except for cases of amenorrhea accompanying severe flares, renal insufficiency-related hypofertility, and ovarian failure secondary to cyclophosphamide (CTX) therapy. 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 ovarian hyperstimulation syndrome (OHSS). Friendly ovarian stimulation, single embryo transfer, avoidance of OHSS, administration of adjuvant therapy, and use of natural E2 or P through a nonoral 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 on which to discourage ART, especially due to the high risk of complications for both mother and fetus during pregnancy and puerperium.

Conclusion(s): Ovarian stimulation for ovulation induction and IVF seems to be safe and successful in well-selected women with SLE and antiphospholipid syndrome. (Fertil Steril 2009;92:1803–10. ©2009 by American Society for Reproductive Medicine.)

Key Words: Systemic lupus erythematosus, antiphospholipid syndrome, ovarian stimulation, infertility, IVF, pregnancy

SYSTEMIC LUPUS ERYTHEMATOSUS
Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory, autoimmune disease of unknown origin characterized by the production of nonorgan-specific autoantibodies and a broad spectrum of clinical and immunological manifestations that can involve joints, kidneys, serous surfaces, and vessel walls. The course of SLE is highly variable, but exacerbation and remission periods are often present (1–4).

The prevalence of this disease ranges from approximately 40 cases per 100,000 persons among Northern Europeans, to more than 200 per 100,000 of the black population in the United States and the United Kingdom, and is low in most African countries (2, 5). The disease also tends to be more severe among the black population (2). Systemic lupus erythematosus is much more common in women, with a female-to-male ratio of 9:1, and a peak onset during childbearing ages (4, 6). In the United States the number of patients with lupus exceeds 250,000 (5). The life expectancy of such patients has improved from an approximate 4-year survival rate of 50% in the 1950s to a current 15-year survival rate of 80%. Even so, a patient in whom lupus is diagnosed at 20 years of age continues to have a 1 in 6 chance of dying by 35 years (5). Death is most often caused by the active disease or infection in young people, and from myocardial infarction and stroke due to atherosclerotic vascular disease in older patients. Mortality from SLE is at least three times higher than in the general population (1).

As prognosis has improved, more cases of SLE women at childbearing age are detected. Common presentations range from rash and arthritis through thrombocytopenia and anemia to serositis, nephritis, seizures, and psychosis. The differential diagnosis of the disease is especially important in women in their reproductive period (15–50 years old) (5). The etiology of the disease is unknown, but the role of female hormones is unquestionable, as 90% of those affected are women. New evidence has been provided by recent research. In a randomized trial
performed in menopausal women with SLE, the administration of
hormonal replacement therapy (HT) containing conjugated estrogens
(E) and P significantly increased (odds ratio [OR]: 1.34;)

hormonal replacement therapy (HT) containing conjugated estrogens
performed in menopausal women with SLE, the administration of
significantly higher proportions with respect to controls(12).

control study involving children and young adults showed that anti-
American College of Rheumatology must be met (Table 1)(1, 2).

sensitivity), 4 of the 11 clinical or laboratory criteria described by the
complement components—C1q, C2, and C4(5). Curiously, a case-
lupus, as well as null alleles that cause deficiency of one of the early
ularly HLA-A1, HLA-B8, and HLA-DR3, have been linked to
are concordant for the disease, but only 2% of dizygotic twins(9).

Many genes that probably contribute to lupus have been identified
families in which multiple members have the disease, with eight
susceptibility loci located in chromosomes 1, 2, 4, 6, 12, and 16 (10,
11). Genes of the major histocompatibility complex (MHC), partic-
arily HLA-A1, HLA-B8, and HLA-DR3, have been linked to
us, as well as null alleles that cause deficiency of one of the early
complement components—Clq, C2, and C4 (5). Curiously, a case-
control study involving children and young adults showed that anti-
Epstein Barr virus antibodies were present in 99% and Epstein Barr
virus DNA was present in 100% of patients with lupus, which were
significantly higher proportions with respect to controls (12).

For the correct diagnosis of SLE (95% specificity and 85% sen-
sitivity), 4 of the 11 clinical or laboratory criteria described by the
American College of Rheumatology must be met (Table 1) (1, 2).
Treatment of the disease includes nonsteroidal anti-inflammatory
drugs, glucocorticoids, and immunomodulators or immunosuppres-
sive/cytotoxic medications, such as hydroxychloroquine, azathiop-
rine, methotrexate (MTX), and cyclophosphamide (CTX) (1).
Cyclophosphamide is very important from the point of view of re-
production, because it constitutes one of the immunosuppressant
drugs of choice for the treatment of severe SLE and induces ovarian
failure by depletion of ovarian oocytes (13). In humans the size of
the ovarian reserve is definitively fixed at birth and decreases dras-
tically with age (14). Intermittent pulse CTX is widely used for both
renal and major extrarenal manifestations of the disease (15). Daily
oral CTX administration causes amenorrhea within a year, lead-
to permanent ovarian failure in more than 70% of patients. Monthly
IV pulse CTX can also cause amenorrhea in up to 45% of patients,
depending on the dose and timing with regard to the menstrual cycle,
being less harmful when monthly IV doses are administered during
menses (16). Cotreatment with oral contraceptive (OC) pill or
GnRH agonists, or ovarian or oocyte cryopreservation should be rec-
ommended to preserve future fertility (15). The GnRH agonists are
preferable to the OC pill as the former have been shown to minimize
the gonadotoxic effect of CTX pulsatile treatment (17–19), and the
OC pill may increase disease activity and the risk of thrombosis.
The risk of amenorrhea is highest in women more than 31 years of age
(16). In fact, it is difficult to avoid sustained amenorrhea in women
more than 31 years, even with very short IV CTX courses. Azathi-
oprine does not alter fertility and chlorambucil has not been clearly
implicated, although the number of patients studied to date has been
limited. The remainder of the cytotoxic agents used in SLE treat-
ment has not been related to infertility (16).

### TABLE 1

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Laboratory criteria</th>
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<tbody>
<tr>
<td>1. Malar rash</td>
<td>9. Hematologic disorder</td>
</tr>
<tr>
<td>2. Discoid rash</td>
<td>Hemolytic anemia with</td>
</tr>
<tr>
<td>3. Photosensitivity</td>
<td>reticulocytosis OR</td>
</tr>
<tr>
<td>4. Oral ulcers</td>
<td>Leukopenia OR</td>
</tr>
<tr>
<td>5. Nonerosive arthritis</td>
<td>Lymphopenia OR</td>
</tr>
<tr>
<td>6. Pleuritis or pericarditis</td>
<td>Persistent proteinuria</td>
</tr>
<tr>
<td>7. Renal disorder</td>
<td>OR</td>
</tr>
<tr>
<td>8. Neurologic disorder</td>
<td>Seizures OR</td>
</tr>
<tr>
<td>9. Hematologic disorder</td>
<td>Psychosis OR</td>
</tr>
<tr>
<td>10. Immunologic disorder</td>
<td>Antiphospholipid antibodies</td>
</tr>
<tr>
<td>11. Antinuclear antibodies</td>
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</tbody>
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ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an acquired thrombophilic dis-
order in which autoantibodies are produced to a variety of phospho-
lipids and phospholipid-binding proteins (20). The criteria for the
correct diagnosis of the APS have recently been redefined by Miya-
kis et al. (21) (Table 2). According to this new classification, at least
one clinical and one laboratory criteria must be met. The clinical
criteria are similar to previous international consensus (22) and in-
clude vascular thrombosis of any vessel and pregnancy morbidity,
such as recurrent early miscarriage, fetal death, or preterm delivery
(<34 weeks) caused by placental insufficiency, eclampsia, or severe
preeclampsia. However, the new laboratory criteria are stricter,
therefore the persistent presence of lupus anticoagulant or antiphos-
pholipid antibodies more than 12 weeks apart is necessary. On the
other hand, antiphospholipid antibodies do not only include IgM or
IgG anticardiolipin antibodies (ACAs) but also anti-β2 glycopro-
ine I antibodies, and in higher titres. In fact, medium-to-high titres
are currently considered from 40 GPL or MPL or >99th centile.
Therefore, following the current criteria, some previously defined
APS would be considered false diagnoses. The objective of the new
criteria is to avoid overdiagnosis and the consequent overtreat-
ment of the syndrome. In addition, some frequently associated fea-
tures are not included in the new revised classification because they
are not specific to patients with APS. The adoption of these features
as independent criteria for definite APS may decrease diagnostic
specificity (Table 3) (21).

The prevalence of both lupus anticoagulant and ACAs is about
1%–5% in healthy young subjects (20). TheAPS is more common
in women, with a female-to-male ratio of 5:1, and a mean age at di-
agnosis of 31 years (15–85 years) (23). The risk of thrombosis
ranges from 0.5%–30% (24). Classically, a differentiation between
primary and secondary APS has been made, with the latter being re-
lated to several pathologic conditions, such as autoimmune diseases
(SLE, rheumatoid arthritis), infection (leprosy, parvovirus B19, hu-
mnan immunodeficiency virus [HIV], hepatitis C, cytomegalovirus),
hematological diseases, hemodialysis, malignancy, and drugs
hydralazine, phenytoin, quinidine, cocaine). Because the clinical manifestations of thrombosis are similar, this distinction has recently been eliminated and replaced by two groups of patients—those with and those without the presence of other risk factors for arterial or venous thrombosis (20, 21).

This article seeks to provide an overview of the relationship between SLE, APS, and infertility, as well as a description of the risks associated with ovarian stimulation for assisted reproduction (ART) in the affected patients. Based on the information obtained, guidelines for the safe performance of ART will be suggested, including a list of situations in which treatment should be discouraged.

SLE, APS, AND INFERTILITY

The first question to answer is whether SLE or APS are related to infertility in women. According to recent evidence autoimmunity cannot be considered a likely cause of primary infertility. Nonhe-
medical complications in women with established SLE or APS (36). In this way, some isolated case reports have described health complications, such as transverse myelopathy and fatal pulmonary embolism (39), lupus flare (40), venous thrombosis (inferior vena cava, subclavian, jugular, renal veins) (41), and arterial thrombosis (brain, heart) (42–45), ascribing the development of these thromboembolic complications to the presence of ovarian hyperstimulation syndrome (OHSS). However, there are very few case reports of complications in women with SLE or APS undergoing OI and COH, in comparison with the thousands of ART cycles that are performed every year all around the world. Even when one assumes that thrombosis or other problems are under-reported, the overall risk continues to seem small (46).

Only two previous studies, both retrospective, have assessed a group of women affected by these diseases. The first one (47) included 17 women with primary APS or SLE who underwent 63 cycles of OI or IVF, using different drugs for ovarian stimulation (clomiphene citrate [CC], urinary FSH, urinary hMG, and GnRH agonists). Seven patients, in whom 16 cycles were performed, presented with SLE. Three of these 16 cycles (19%) and thus, 3 of the 7 women (43%), showed a mild increase in the lupus activity in the form of discoid rash, ulcers, herps, arthritis, myositis, alopecia, or vasculitis. This increased activity was observed even with CC and in women with or without cotreatment with prednisone. On the other hand, 2 of these 16 cycles (13%) and thus, 2 of the 7 women (29%) presented with OHSS, but only in a mild form, described as enlarged ovaries and abdominal discomfort. Considering that the mild flare frequency per 9-month period in nonpregnant women is 40%–80%, and that the mild OHSS in healthy population appears in up to 33% of women, the incidence of complications in the study group was not higher than expected. In addition, 10 women with primary APS who underwent 47 cycles did not present with any complications. However, it should be pointed out that all the subjects were in clinical remission when ovarian stimulation was initiated. In addition, 4 of the 7 women with SLE and the 10 women with primary APS were undergoing prophylactic therapy (prednisone–immunosuppressants and prednisone–heparin–aspirin, respectively).

The second study (28) included 21 women with SLE or APS who underwent 114 OI or IVF cycles, also stimulated with several drugs (CC, urinary FSH, urinary hMG, and GnRH analogues). The disease had been diagnosed beforehand in only 45 cycles. In the other 69 cycles the disease was discovered due to the emerged complications after ovarian stimulation or during pregnancy. The study population included women with SLE (n = 9; 62 cycles), primary APS (n = 8) or secondary APS (to SLE) (n = 4). Lupus flare occurred in 13 of the 62 cycles (21%) in SLE women: in 3 of 29 cycles with known disease (10%), and in 10 of 33 cycles with unknown disease (30%). The incidence of lupus flare was three times higher when the cycle was unplanned than when it was planned. “Nonplanned” means that the disease was not previously controlled because it was unknown and, therefore, women were not receiving prophylactic therapy with prednisone, immunosuppressants, or anticoagulants (aspirin, heparin) when ovarian stimulation was initiated. Finally, the increase in lupus activity was four to five times higher with gonadotropins than with CC, probably due to the increased serum E₂ concentrations achieved, but pregnancy rates (PR) were six times lower with CC (25% vs. 4%, respectively). Regarding thrombotic events, only two venous thromboses were diagnosed in the 69 women with unknown disease who underwent an ovarian stimulation with gonadotropins. No cases of OHSS were detected.

Some conclusions can be obtained from these two studies: [1] when the disease is known, a planned ovarian stimulation with co-administration of prophylactic therapy (especially, anticoagulation for thrombotic complications and corticosteroids for lupus activity) during a remission phase can reduce the complication rate in these patients, leading to a safe and successful treatment; and [2] when the disease is unknown there is an increased risk of thrombotic or lupus flare complications. Therefore, knowledge of the expected prevalence of undiagnosed lupus in the infertile population is of interest in determining the need for screening before the OI/COH. Only one study has estimated this prevalence in a cohort of infertile women, giving a result of 1.5% (3). However, the sample size considered was quite small (136 patients undergoing IVF) and could have led to an overestimation. Larger studies are required to explore this issue. In addition, around 15% of unknown SLE cases are diagnosed during pregnancy (26) and not before, due to several trigger factors that will be later discussed.

Perhaps the most threatening condition associated with ovarian stimulation in women with SLE and APS is thrombosis. In ovarian stimulation several clotting changes have been described, such as an increase in fibrinogen concentration closely related to the increase in E concentration, an increase in von Willebrand factor, a reduction in antithrombin III, an increase in whole blood clot lysis time, platelet increase, and a decrease in fibrinolysis activity (37, 48–50). These changes would induce a relatively hypercoagulable state. However, the absolute risk of thrombosis during ovarian stimulation is slight or only modest because the predominant E involved is E₂ and not a synthetic E, and also because of the relatively short duration of elevated E's (46). Therefore, the risk of thrombosis would be really increased only in women with thrombophilia or a history of a thromboembolic event (37).

Chan and Dixon (41) recently performed a systematic review of thromboembolic complications (TEC) related to ART, from 1966–2006. They included 58 articles, case reports, or series, with information relating to 71 episodes of TEC in association with ovarian stimulation or ART in 70 women. Different drugs were used (FSH, CC, GnRH, GnRH agonists). Eighty percent of the cases of TEC appeared in IVF cycles. In all but one case (70/71) thrombosis occurred after hCG administration. Progesterone for luteal phase support was reported in 19 women. The risk of TEC was 10 times higher with IVF than with ovulation induction. Seventy-nine percent of thrombosis was associated with OHSS. The OHSS was reported in 95% of all the cases involving arterial thrombosis and in 70% of women with venous thrombosis. When the investigators searched for the risk factors for thrombosis in this population, inherited thrombophilia was present in one-third of the women tested (especially associated with venous thrombosis), 24% presented an advanced age (≥35 years), and three isolated cases showed concomitant malignancy or central venous catheters, all associated with venous thrombosis. Therefore, no case of SLE or isolated APS was reported. High titres of IgM antiphospholipid antibodies were detected in only one woman, but with a concomitant low protein S concentration. Similarly, another recent review (45), which included 34 cases of arterial thrombosis after ART using gonadotropins with and without GnRH agonists, arrived at the same conclusion. Virtually, all cases of TEC appeared after hCG administration. In said review, only 7 of the 34 cases considered presented risk factors for thrombosis: smoking in 4 cases, decreased protein S in 1 case, and antiphospholipid antibodies in 1 case. Two more cases of positive ACAs were detected, but one was associated with smoking and the other with low protein S, as previously commented. Again, thrombosis tended to develop as part of an overt OHSS. Because several approaches were used for ovarian stimulation, no conclusive remarks can be made whether one approach is less dangerous than another with regard to OHSS and consequent
thrombosis. Obviously, pre-existing congenital or acquired thrombophilic states are likely to play a role on the risk of thrombosis, but such contributory factors are apparently absent in the majority of cases.

Although further studies are needed to obtain conclusive evidence, when SLE is in remission, with no deep organ involvement and no association with APS, or the APS is present but with low titres of autoantibodies or a prophylactic therapy is associated, OI and COH seem to be safe and successful. However, high rates of maternal and fetal complications may appear in these women. Hence, before initiating an ovarian stimulation protocol, a consideration of the possible complications during pregnancy should be mandatory (6, 28, 37, 47).

HOW TO PERFORM THE OVARIAN STIMULATION IN WOMEN WITH SLE/APS

Some guidelines for the adequate ovarian stimulation in women with SLE/APS can be drawn from the information described in the previous section. The first question is whether the OC pill can be used in these patients for cycle programming. Obviously, progestogen-(progestin)-only OC pills (minipill) present a lower risk of thrombosis and do not induce an increase in the rate of lupus flares (6), but they are not useful in ovarian stimulation. On the other hand, E-containing OC pills, which are commonly used, could induce (1.4 times) (51) or exacerbate (2 times) the lupus activity (52). However, it should be pointed out that most of the studies that provide this evidence are old and used OC pills with high doses of Es (50 μg). In addition, relevant experience is scarce, as these drugs are infrequently prescribed in women affected by the disease (6). That said, two recent randomized trials have shown that OCs with lower doses of Es (30–35 μg) do not seem to increase the risk of a flare among women with SLE in whom the disease is stable (53, 54). Estrogen-containing OC pills could also increase the risk of venous and arterial thrombosis (2–3 times), especially in the presence of APS or other thrombophilias (55, 56). However, the impact of E on various clotting factors is dose-dependent with little, if any, effect with doses of ethinylestradiol <50 μg (6, 57). In an inactive or stable/moderate disease, without high titres of antiphospholipid antibodies, negative lupus anticoagulant, absence of risk factors or previous clinical history of thrombosis, and no previous exacerbation of the lupus activity with administration of Es, combined OC pills may be administered, using the lowest possible dose of ethinylestradiol (30–35 μg) (Table 4) (6).

With regard to ovarian stimulation, despite the lack of studies about the benefits or risks of different ovarian stimulation regimens or protocols, a friendly ovarian stimulation is always advisable to avoid high serum E₂ concentrations. In ovulation induction in the case of anovulation, anti-Es constitute the first line of treatment (58), with CC being the drug of choice. If this treatment fails, in case of amenorrhea, pulsatile GnRH is preferable to gonadotropins as it does not carry any risk of OHSS (58). In COH, gonadotropins should be used sparingly and with continuous and close follow-up. With respect to IVF, one study compared the impact of two formulations of the same drug, urinary versus recombinant FSH, on hemostasis in a healthy infertile population (59). Recombinant FSH did not influence coagulation and fibrinolysis significantly, as had previously been reported for urinary gonadotropins, and the moderate changes induced by both treatments were no longer detectable after 4 weeks. At present, no specific type of gonadotropin has been shown to offer a clear advantage in the prevention of thrombosis. Considering that most cases of TEC appear after hCG administration and in association with overt OHSS (41, 45), the main aim in women affected by SLE/APS should be to avoid OHSS by using available preventive strategies, such as mild stimulation protocols, cycle cancellation, coasting, administration of lower doses of hCG or GnRH agonists (when GnRH antagonists are used) for oocyte pick-up, embryo freezing, or dopaminergic agonists (60, 61). In addition, single embryo transfer is advisable to reduce β-hCG serum levels in the initial stages of pregnancy, which are related to the onset and severity of a “late” OHSS (62). In addition, pregnancy complications are increased in SLE/APS women with multiple pregnancies (25, 47, 63). In very high-risk patients, natural cycles in combination with heparin treatment are proposed before surrogacy is considered (37).

Coadjuvant therapy (anticoagulation, corticosteroids, immunosuppressants) should be considered during and after ovarian stimulation for the prevention of thrombosis or lupus flares. With respect to anticoagulation in women with SLE and APS, the most appropriate approach seems to be the following (46, 58); [1] women with antiphospholipid antibodies and no history of thrombosis should not be treated with heparin before ovum retrieval. The efficacy of aspirin therapy for reducing the risk of thrombosis in this phase remains unproven (64). In such women, heparin thromboprophylaxis should be advised from the time of embryo transfer, to reduce the risk of thrombosis, which increases from the beginning of the luteal phase; [2] women with antiphospholipid antibodies and a history of thrombosis should be switched from oral anticoagulant therapy (mainly warfarin) to therapeutic doses of heparin for ovarian stimulation. To reduce bleeding complications, heparin should be discontinued 12–24 hours before ovum retrieval and started again 6–12 hours later when the patient is clinically stable. In both cases, heparin is to be maintained until the day of the pregnancy test and should be continued in the case of pregnancy. Low dose aspirin should be added, but interrupted 5–7 days before oocyte retrieval to avoid bleeding. In women with only SLE and not APS, anticoagulation is not currently recommended, but anti-inflammatory therapy (corticosteroids, immunosuppressants) should be considered or

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Laboratory criteria</th>
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</thead>
<tbody>
<tr>
<td>1. Inactive or stable/moderate disease</td>
<td>1. No lupus anticoagulant disease</td>
</tr>
<tr>
<td>2. No history of venous or arterial thrombosis</td>
<td>2. No high titres of any antiphospholipid antibody isotype (IgG &gt;40 GPL, IgM &gt;40 MPL, IgA &gt;50 APL)</td>
</tr>
<tr>
<td>3. No history of lupus exacerbation with estrogens</td>
<td></td>
</tr>
<tr>
<td>4. Nonsmoker</td>
<td>Consider progestogen-only oral contraceptives</td>
</tr>
<tr>
<td>5. Normotensive</td>
<td>OR Use the lowest dose of ethinylestradiol (≤35 μg) in combined oral contraceptives</td>
</tr>
</tbody>
</table>

Adapted from reference (6).

Increased to reduce lupus flares, especially when gonadotropins are used (28, 58).

In ovum donation and transfer of frozen embryos, the natural cycle is preferable than the administration of exogenous Es for endometrial preparation (37). When Es are used, natural Es (E2) are less procoagulant than synthetic Es and, thus present a lower risk of thrombosis (6, 36). Similarly, the transdermal route should be the first option because it avoids the first-passage effect of oral Es, thereby influencing coagulation to a lesser degree (6, 36, 65). Luteal phase support has not been evaluated in detail in women with lupus or APS. However, P clearly presents a lower risk of thrombosis than hCG, as it is not related to the occurrence of OHSS. Based on studies performed in menopausal women undergoing HT, natural P is also preferable to synthetic P (66). Vaginal administration should be a better route than oral administration because it also avoids the first-passage effect in the liver.

Table 5 summarizes the guidelines for ovarian stimulation in women with SLE or APS.

WHEN TO DISCOURAGE ART IN WOMEN WITH SLE/APS

In women affected by SLE or APS, ovarian stimulation seems to be safe and successful when the disease is in clinical remission and appropriate prophylactic anticoagulant or anti-inflammatory therapy is administered (6, 27, 46, 58, 64). Hence, the most dangerous period is not ovarian stimulation but pregnancy, in which the rates of fetal and maternal complications are high (6). Therefore, the main reason for discouraging ART in affected patients is the high risk of a severe complication during pregnancy or puerperium. In this way, care providers working in the field of human reproduction should be familiar with the impact of pregnancy on SLE and APS, and with the impact of SLE and APS on pregnancy.

The three main implications of pregnancy on SLE are: [1] exacerbation of SLE and increased likelihood of a flare, which occurs in 18%–74% of women according to the findings of different studies (4, 26, 27, 31). The type of flare usually follows previous patterns (4) and may occur in late pregnancy or puerperium in 46.6% of cases (67); [2] renal involvement is one of the most serious complications of SLE, and there is a risk of deterioration of renal function in pregnancy, particularly in patients with hypertension, heavy proteinuria, or high baseline serum creatinine concentration (4). Renal impairment occurs in 3%–27% of cases of lupus nephritis flare, with the renal damage being irreversible in up to 10% (68, 69); and [3] increased risk of maternal thrombosis (venous and arterial), especially in the puerperium and when antiphospholipid antibodies are present (70). There are three main implications of SLE on pregnancy: [1] increased risk, by 2–6 times, of complications related to placental insufficiency, including miscarriage, intrauterine death, hypertension, preeclampsia, intrauterine growth retardation, low birth weight, and preterm delivery (4, 26, 31, 47, 64). These conditions are especially prevalent in the presence of positive antiphospholipid antibodies (in 30%–40% of women with lupus) or renal disease, even when quiescent (4, 27, 64, 68); [2] in women with positive anti-Ro or anti-La antibodies, fetal heart block and cutaneous neonatal lupus appears in 1%–3% and 16% of fetuses, respectively (4, 5, 26). Congenital heart block can appear as early as the 16th week of gestation, and may lead to fetal demise. The risk of congenital heart block increases to 15%–20% if a previous child has been affected and to 50% if two children have been affected (4). Fetal congenital heart block is observed in 2%–4.5% of SLE pregnancies (27). Anti-Ro and anti-La antibodies are present in 30% and 10% of SLE women, respectively (26); and [3] pulmonary hypertension, reported in up to 14% patients with lupus, is associated with a high risk of maternal death (71).

Based on this information, the most favorable scenario for pregnancy to take place in women with lupus is when the disease has been inactive for at least 6 and, if possible, 12 months, and in the absence of arterial and pulmonary hypertension, renal involvement, and antiphospholipid or anti-Ro/anti-La antibodies (4, 26, 28, 31). Therefore, prenatal counseling is essential to establish a prognosis based on renal function, blood pressure, and titres of antiphospholipid, anti-Ro, and anti-La antibodies. In this way, reliable medical advice can be offered for encouraging or discouraging this pregnancy, regardless the method of conception used (spontaneously or by ART). On the other hand, the most appropriate moment for determining the potential hazards of the drugs prescribed for the treatment of SLE for the mother and fetus is before conception. In pregnancy and lactation some immunosuppressants, such as CTX, mycophenolate mofetil, MTX, and leflunomide, are contraindicated due to their teratogenicity and embryotoxicity (4). Table 6 shows the situations in which pregnancy should be discouraged.

CONCLUSIONS

Based on this information, ART does not appear to harm selected women with pre-existing autoimmune diseases. The OHSS and
multiple gestations constitute independent risks. Our objective must be a healthy live born in a mother free of complications, as most complications occur during pregnancy and puerperium, and not before. Stable autoimmune diseases without major organ damage do not seem to affect ART outcome. When controlled, clinically and medically, SLE and APS do not increase complications during ART. Women with SLE receiving an adequate prenatal counseling, pregnancy monitoring, and prophylactic/therapeutic actions achieve high rates of live and healthy births, ranging from 66%–85% (26).

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