

Ovarian stimulation for ovulation induction
and in vitro
fertilization in patients with systemic lupus
erythematosus and antiphospholipid
syndrome

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SYSTEMIC LUPUS ERYTHEMATOSUS



SLE

- a chronic, multisystem, inflammatory, autoimmune disease of unknown origin
- production of **nonorgan-specific autoantibodies** and a broad spectrum of clinical and immunological manifestations
 - involve joints, kidneys, serous surfaces, and vessel walls



- Prevalence:

- approximately 40/100,000 persons among Northern Europeans
- 200/100,000 of the black population in the United States and the United Kingdom
- low in most African countries (Tends to be more severe among the black population)



- Much more common in women (F:M=9:1)

- a peak onset during childbearing ages

- Cause of death:

- Young people: active disease or infection
- Older patients: myocardial infarction and stroke due to atherosclerotic vascular disease.

- Mortality from SLE is at least **three times higher** than in the general population



- As prognosis has improved, more cases of SLE women at childbearing age are detected.
- Common presentations
 - rash and arthritis through thrombocytopenia and anemia
 - serositis, nephritis, seizures, and psychosis.
- The etiology of the disease is unknown, but the role of **female hormones** is unquestionable, as 90% of those affected are women.



- In a randomized trial (*menopausal women with SLE*) the administration of HT containing conjugated estrogens (E) and P **significantly increased** the incidence of **mild-to-moderate flares (lupus activity)**

Buyon JP, et al. Ann Intern Med 2005;142:953–62.

- In a study of a pair of monozygotic twins discordant for SLE:
 - the unaffected twin : underwent castration at 21 y/o for ovarian cancer and did not receive ovarian replacement therapy for the following 23 years
 - Affected twin: continuous ovarian function developed SLE

- drug-induced lupus : procainamide, hydralazine, and quinidine
- Ultraviolet radiation: the **environmental factor** most linked to lupus (etiologic factor: as a photosensitive rash is a criterion for diagnosis of the disease)
- Many genes that probably contribute to lupus have been identified in families in which multiple members have the disease → 8 susceptibility loci located in chromosomes *1, 2, 4, 6, 12, and 16*
- Genes of the MHC, particularly **HLA-A1, HLA-B8, and HLA-DR3** → linked to lupus



TABLE 1**Classification criteria for SLE.**

Clinical criteria	Laboratory criteria
1. Malar rash	9. Hematologic disorder
2. Discoid rash	Hemolytic anemia with reticulocytosis
3. Photosensitivity	OR
4. Oral ulcers	Leukopenia
5. Nonerosive arthritis	OR
6. Pleuritis or pericarditis	Lymphopenia
7. Renal disorder	OR
Persistent proteinuria	Thrombocytopenia
OR	10. Immunologic disorder
Cellular casts	Anti-DNA
8. Neurologic disorder	OR
Seizures	Anti-Sm
OR	OR
Psychosis	Antiphospholipid antibodies
	11. Antinuclear antibodies

Adapted from reference (1).

Bellver and Pellicer. Ovarian stimulation in SLE and antiphospholipid syndrome. Fertil Steril 2009.

- For the correct diagnosis of SLE (95% specificity and 85% sensitivity), **4 of the 11 clinical or laboratory criteria** described by the American College of Rheumatology must be met

- Treatment :
 - NSAIDs
 - Glucocorticoids
 - immunomodulators or immunosuppressive/ cytotoxic medications, such as hydroxychloroquine, azathioprine, methotrexate (MTX), and cyclophosphamide (CTX)
- CTX: very important from the point of view of **reproduction** → induces ovarian failure by depletion of ovarian oocytes
- **Intermittent pulse CTX** : used for both renal and major extrarenal manifestations of the disease.
- **Daily oral CTX** : causes **amenorrhea within a year** → **permanent ovarian failure** in > **70%** of patients.
- **Monthly IV pulse CTX** : cause **amenorrhea in > 45%** of patients, depending on the dose and timing with regard to the menstrual cycle (*less harmful when monthly IV doses are administered during menses*)



- preserve future fertility :
 - Cotreatment with oral contraceptive (OC) pill or GnRH agonists
 - ovarian or oocyte cryopreservation
- The **GnRH agonists are preferable** to the OC pill
 - GnRH agonist **minimize the gonadotoxic effect** of CTX pulsatile treatment
 - OC pill may **increase disease activity** and the **risk of thrombosis**.
- The risk of amenorrhea is highest in women **> 31 y/o**
- In fact, it is difficult to avoid sustained amenorrhea in women > 31 years, even with very short IV CTX courses



ANTIPHOSPHOLIPID SYNDROME



APS

- Antiphospholipid syndrome (APS) is an **acquired thrombophilic disorder** in which autoantibodies are produced to a variety of phospholipids and phospholipid-binding proteins.
 - The prevalence of both lupus anticoagulant and ACAs (anti-cardiolipin antibodies) is about 1%–5% in healthy young subjects
- The criteria for the correct diagnosis of the APS have recently been redefined by Miyakis et al. (Table 2)



TABLE 2

Classification criteria for antiphospholipid syndrome.

Clinical criteria

1. Vascular thrombosis of any vessel in any tissue or organ
2. Pregnancy morbidity
 - ≥ 1 fetal death (>10th week of gestation) of morphologically normal fetuses
 - ≥ 3 unexplained consecutive spontaneous abortions (<10th week of gestation)
 - ≥ 1 premature delivery of morphologically normal neonate <34th week of gestation because of: eclampsia, severe preeclampsia, or placental insufficiency

Laboratory criteria

1. Positive plasma lupus anticoagulant (in ≥2 occasions at least 12 weeks apart)
2. Positive medium or high titres of IgG or IgM anticardiolipin antibodies (>40 GPL or MPL, or > the 99th percentile) in serum or plasma (in ≥2 occasions at least 12 weeks apart)
3. Positive titres of IgG or IgM anti-β₂ glycoprotein-I antibodies (> the 99th percentile) in serum or plasma (in ≥2 occasions at least 12 weeks apart)

Adapted from reference (18).

Bellver and Pellicer. Ovarian stimulation in SLE and antiphospholipid syndrome. Fertil Steril 2009.

•The new laboratory criteria are **stricter** → some previously defined APS would be considered **false diagnoses**.

•The objective of the new criteria → avoid overdiagnosis and the consequent overtreatment of the syndrome

- The adoption of some features as independent criteria for definite APS may **decrease diagnostic specificity** → not included in the new revised classification



TABLE 3

Features associated with antiphospholipid syndrome not included in the new revised criteria (18).

Heart disease

Vegetations, valve thickening, and dysfunction

Coronary heart disease

Livedo reticularis and other skin manifestations

Thrombocytopenia

Nephropathy

Neurologic manifestations

Transient cerebral ischemia and stroke

Physical disability in the elderly

Cognitive dysfunction – dementia?

Migraine

Epilepsy

Transverse myelopathy

Beliver and Pellicer. Ovarian stimulation in SLE and antiphospholipid syndrome. Fertil Steril 2009.



- The APS is more common in women (**F:M = 5:1**)
- a mean age at diagnosis of 31 years (15–85 years)
- The risk of thrombosis ranges from 0.5%–30%.
- primary VS. secondary APS :
 - the latter being related to several pathologic conditions, such as
 - *autoimmune diseases (SLE, rheumatoid arthritis)*
 - *infection (leprosy, parvovirus B19, human immunodeficiency virus [HIV], hepatitis C, cytomegalovirus)*
 - *hematological diseases, hemodialysis, malignancy*
 - *drugs (hydralazine, phenytoin, quinidine, cocaine).*
 - the clinical manifestations of thrombosis are **similar** → distinction has been eliminated → replaced by two groups of patients :
 - *with and without the presence of other **risk factors for arterial or venous thrombosis***



- This article seeks to provide an overview of the
 - **relationship** between SLE, APS, and infertility
 - the **risks** associated with ovarian stimulation for assisted reproduction (ART) in the affected patients
 - 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

- Nonrheumatic autoimmune thyroid, ovary, and adrenal failure do cause infertility by interfering with endocrine function.
- However, except for drug-induced (e.g. CTX) ovarian failure, **primary infertility is not common among patients with rheumatic diseases**
- Fertility is known to be normal in women with SLE, except for three situations:
 - [1] amenorrhea accompanying severe flares
 - [2] renal insufficiency-related hypofertility
 - [3] ovarian failure secondary to CTX therapy
 - *The two first usually appear in cases of severe lupus.*



- Some retrospective reports : a **relationship between antiphospholipid antibodies and infertility and poor ART outcome** → **However** → recent studies have **not detected** a higher prevalence of these autoantibodies in infertile women
- Recently, our group **failed to observe** a higher prevalence of lupus anticoagulant or ACAs in women with unexplained infertility than in a control group of fertile egg donors
- the presence of antiphospholipid antibodies does not seem to affect ART outcome → therapy is not justified
- The presence of antiphospholipid antibodies among infertile women is likely to be a **part of a generalized autoimmune disturbance** associated with infertility



RISKS OF OVARIAN STIMULATION IN WOMEN WITH SLE/APS



- The complications described for OI and COH in women with SLE or APS seem to be the result of the **elevated serum 17b-E2 concentrations achieved** (regardless of the type of drug used for stimulation)
- the levels of circulating 17b-E2 after such treatments may exceed menstrual levels by 2- to 10-fold → induce, unmask, or exacerbate pre-existing SLE or most commonly induces medical complications in women with established SLE or APS
- There are very few case reports of complications in women with SLE or APS undergoing OI and COH



- Only two previous studies (retrospective) have assessed a group of women affected by these diseases
- 1st:
 - 17 women with primary APS or SLE → 63 cycles of OI or IVF, using different drugs for ovarian stimulation → All the subjects were in **clinical remission** when ovarian stimulation was initiated!
 - 7 patients (16 cycles) with SLE: 3/16 cycles (19%) { 3/7 women (43%)} showed a **mild increase in the lupus activity** (in women with or without cotreatment with prednisone)



- 2/16 cycles (13%) {2/7 women (29%)} presented with OHSS (only in a mild form: enlarged ovaries and abdominal discomfort) → the incidence of complications was not higher than expected (mild OHSS up to 33% of normal population women)
- 10 patients (47 cycles) → primary APS → did not present with any complications.
- 4/7 women with SLE and the 10 women with primary APS were undergoing **prophylactic therapy** (prednisone–immunosuppressants and prednisone–heparin–aspirin, respectively).



- 2nd:

- 21 women with SLE with several cycles on GnRH analog
- 45 cycles : d
- 69 cycles : d complications pregnancy.
- women with SLE secondary APS (to
- Lupus flare :
 - 13/62 cycles (21%) in SLE women
 - 3/29 cycles (10%) with known disease
 - 10/33 cycles (30%) with unknown disease

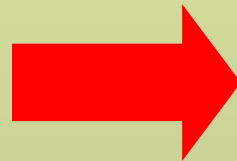
Incidence : 3 times higher when the cycle was unplanned (“Nonplanned” = the disease was not previously controlled because it was unknown → not receiving prophylactic therapy with when ovarian stimulation was initiated)



- 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).
- 2 venous thromboses in the 69 cycles 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 coadministration of **prophylactic therapy**: during a remission phase can **reduce the complication rate**
 - [2] when the disease is **unknown**, 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



- one study has estimated : giving a result of 1.5% → sample size considered was quite small (136 patients) → overestimation.

- 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:
 - an increase in fibrinogen concentration closely related to the increase in E concentration
 - an increase in vonWillebrand factor
 - a reduction in antithrombin III
 - an increase in whole blood clot lysis time
 - platelet increase
 - a decrease in fibrinolysis activity
- ➔ induce a relatively hypercoagulable state.



- the absolute risk of thrombosis during ovarian stimulation is slight or only modest
 - the predominant E involved is E2 and not a synthetic E
 - the relatively short duration of elevated Es.
- ➔ risk increased only in women with thrombophilia or a history of a thromboembolic event



- Chan and Dixon : a systematic review of thromboembolic complications (TEC) related to ART (1966–2006)
 - 71 episodes of TEC in association with ovarian stimulation or ART in 70 women → 80% of TEC appeared in IVF cycles.
 - 70/71 thrombosis occurred after hCG administration.
 - risk of TEC: 10 times higher with IVF than with OI
 - 79% thrombosis was associated with OHSS.
 - 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% advanced age (≥ 35 years)
 - 3 cases: concomitant malignancy or central venous catheters(venous thrombosis)



- Another recent review which included 34 cases of arterial thrombosis after ART using gonadotropins with and without GnRH agonists → same conclusion.

Girolami, et al. J Thromb Thrombolysis 2007;24:169–74.


- pre-existing congenital or acquired thrombophilic states → play a role on the risk of thrombosis → 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 titers of autoantibodies or a prophylactic therapy is associated →

OI and COH seem to be safe and successful.



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

- Whether the OC pill can be used in these patients?
- progestogen-(progestin-)only OC pills (minipill)
 - lower risk of thrombosis
 - not induce an increase in the rate of lupus flares.
- E-containing OC pills: induce (1.4 times) or exacerbate (2 times) the lupus activity **BUT:** most of the studies that provide this evidence are **old** and used OC pills with **high doses of Es(50 mg)**.
- 2 recent randomized trials : lower doses of Es (30–35 mg) **do not seem to increase the risk** of a flare among women (*with disease is stable*)
- Estrogen-containing OC pills: increase the risk of **venous and arterial thrombosis** (2–3 times), especially APS (+) or other thrombophilias
- However, the impact of E on various clotting factors is dose-dependent with little if doses of **ethinylestradiol <50 mg**



**not useful in
ovarian
stimulation**

- combined OC pills with using the lowest possible dose of ethinylestradiol (30–35 mg) may be safe:
 - In an inactive or stable/moderate disease
 - without high titers of APA
 - negative lupus anticoagulant
 - absence of risk factors
 - previous clinical history of thrombosis
 - no previous exacerbation of the lupus activity with administration of Es
- a friendly ovarian stimulation is always advisable to avoid high serum E2 concentrations.



- Recombinant FSH did not influence coagulation and fibrinolysis significantly (the moderate changes induced by both treatments were no longer detectable after 4 weeks)
- Most cases of TEC appear **after hCG administration** and in **association with overt OHSS** →
- 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 for oocyte pick-up
 - embryo freezing
 - dopaminergic agonists



- single embryo transfer → reduce b-hCG serum levels in the initial stages of pregnancy
- pregnancy complications are **increased** in SLE/APS women with **multiple pregnancies**
- In very high-risk patients → **natural cycles + heparin treatment** are proposed
- **Coadjuvant therapy** (anticoagulation, corticosteroids, immunosuppressants) : 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:

- [1] APA (+) and history of thrombosis (-)

- No treated with heparin before ovum retrieval
- heparin thromboprophylaxis since the time of ET, to reduce the risk of thrombosis (increases from the beginning of the luteal phase)

- [2] APA (+) and history of thrombosis (+)

- oral anticoagulant therapy (mainly warfarin) → therapeutic doses of heparin for ovarian stimulation.
- heparin DC 12–24 hrs before ovum retrieval and started again 6–12 hours later
- Keep heparin till the day of the pregnancy test, continued in the case of pregnancy.
- Low dose aspirin should be added (interrupted 5–7 days before oocyte retrieval to avoid bleeding)



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

TABLE 5

Guidelines for ovarian stimulation in women with SLE or antiphospholipid syndrome.

Friendly ovarian stimulation

Clomiphene citrate: drug of choice in ovulation induction

Prevent ovarian hyperstimulation syndrome

Single embryo transfer

Coadjuvant therapy: anticoagulation, corticosteroids, immunosuppressants

Transfer of frozen embryos and ovum donation

Natural cycles better than treated cycles

Natural E₂ better than synthetic estrogens

Transdermal route better than oral route

Luteal phase support

Progesterone better than hCG

Natural P better than synthetic progestogens

Vaginal route better than oral route

Bellver and Pellicer Ovarian stimulation in SLE and antiphospholipid syndrome. Fertil Steril 2009.



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
- the most dangerous period is not ovarian stimulation but pregnancy: the rates of fetal and maternal complications are high.
- the main reason for discouraging ART in affected patients : **high risk of a severe complication during pregnancy or puerperium.**



- 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 → may occur in late pregnancy or puerperium in 46.6% of cases
 - [2] **renal involvement** is one of the most serious complications of SLE (*there is a risk of deterioration of renal function in pregnancy : patients with hypertension, heavy proteinuria, or high baseline serum creatinine concentration*)
 - Renal impairment occurs in 3%–27% of cases of lupus nephritis flare, with the renal damage being **irreversible** in up to 10%
 - [3] increased risk of maternal thrombosis (venous and arterial), especially in the **puerperium** and when **antiphospholipid antibodies are present**



- There are three **main implications** of SLE on pregnancy:
 - [1] increased risk (2–6 times) of complications related to **placental insufficiency** → miscarriage, IUFD, hypertension, preeclampsia, IUGR, LBW, and preterm delivery (*especially in the presence APA (+) or renal disease*)
 - [2] positive anti-Ro or anti-La antibodies (*30% and 10% of SLE women*), **fetal heart block and cutaneous neonatal lupus** appears in 1%–3% and 16% of fetuses
 - Congenital heart block can appear as early as the 16th week of gestation, and may lead to fetal demise.
 - Fetal congenital heart block is observed in 2%–4.5% of SLE pregnancies
 - [3] **pulmonary hypertension** (up to 14% patients with lupus) associated with a high risk of **maternal death**



- Based on this information, the **most favorable scenario** for pregnancy to take place in women with lupus is
 - disease has been inactive for at least 6 and, if possible, 12 months,
 - Absence of arterial and pulmonary hypertension, renal involvement
 - Absence of antiphospholipid or anti-Ro/anti-La antibodies
- prenatal counseling is essential to establish a prognosis based on renal function, blood pressure, and titers of antiphospholipid, anti-Ro, and anti-La antibodies.
- 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 → **contraindicated** (teratogenicity and embryotoxicity)



- Table 6 shows the situations in which pregnancy should be discouraged.



TABLE 6


Clinical situations in which ovarian stimulation should be discouraged in women with SLE.

Systemic lupus in acute flare (and 6–12 following months)
Badly controlled arterial hypertension
Pulmonary hypertension
Advanced renal disease
Severe valvulopathy or heart disease
Major previous thrombotic events
Comment on risk of antiphospholipid syndrome and anti-Ro/
anti-La antibodies

Bellver and Pellicer. Ovarian stimulation in SLE and antiphospholipid syndrome. Fertil Steril 2009.



CONCLUSIONS

- ART does not appear to harm selected women with pre-existing autoimmune diseases 
- The OHSS and multiple gestations → independent risks
- 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 → high rates of live and healthy births, ranging from 66%–85%





Thanks for your attention!

