



## Review

# Utilization of hyperestrogenic therapies in systemic lupus erythematosus

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### ABSTRACT

The use of treatments that increase oestrogen levels has usually been deemed risky in lupus patients. Past studies about the utilisation of oral contraceptive drugs and hormone replacement therapy (HRT) have shown contradictory results. More recently, prospective studies about this issue suggest that either oral contraceptives or HRT can be used in patients with stable disease without special risk for increments in clinical activity. Neither has an association with the development of arterial or venous thrombosis been observed. However, in this respect, several methodological limitations preclude establishing definitive conclusions.

Regarding the use of assisted reproduction techniques in lupus patients, only retrospective data are available. Overall they indicate that the real risk of disease exacerbation is quite low, the flares being generally mild when these procedures are performed in patients with stable disease.

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## Utilización de terapias hiperestrogénicas en el lupus eritematoso sistémico

### RESUMEN

La utilización de tratamientos que aumenten los niveles estrogénicos ha sido considerada clásicamente de riesgo en pacientes lúpicos. Estudios relativamente antiguos sobre la utilización de anticonceptivos orales y de tratamiento hormonal sustitutivo han proporcionado resultados contradictorios o inconsistentes. Más recientemente, estudios prospectivos sobre esta problemática sugieren que tanto los anticonceptivos como el tratamiento hormonal sustitutivo pueden ser utilizados en pacientes con enfermedad estable sin riesgo de un aumento en la actividad clínica de ésta. Tampoco se ha observado una asociación al desarrollo de complicaciones tromboembólicas arteriales y/o venosas. Aunque, a este respecto, determinaciones y limitaciones metodológicas imposibilitan el establecer valoraciones definitivas sobre esta problemática.

Con respecto a la utilización de técnicas de fertilización asistida en pacientes lúpicas, todos los datos de que se disponen son de tipo retrospectivo. Globalmente considerados, estos estudios indican que el riesgo real de reagudización de la enfermedad es relativamente bajo y que, en general, no son agudizaciones graves, siempre y cuando estas técnicas se realicen en pacientes con enfermedad estable.

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## Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that is potentially serious and that, although less common than other inflammatory diseases (such as rheumatoid arthritis), cannot be considered as a rare disease.

Its aetiopathogenesis remains unknown despite continuous progress in this field. However, for a long time it has been clear that oestrogens must have some type of promoter or facilitator role in

disease development. Several advances have helped to strengthen this idea. Firstly, the disease affects mainly women of childbearing age, who therefore have high oestrogen levels. Furthermore, studies in lupus murine models have shown how oestrogens accelerate disease development, while anti-oestrogen treatment delays it.<sup>1,2</sup> Epidemiological studies have shown that the risk of suffering SLE increases in individuals who have taken oral contraceptives as hormone replacement therapy (HRT).<sup>3,4</sup> It is also accepted that pregnancy and the postpartum period, the periods when oestrogen

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levels rise, involve the risk of reactivating SLE. Finally, a classic study by Lahita et al demonstrated that SLE patients had a metabolic disorder, the end result of which was the production of more potent oestrogen derivatives.<sup>5</sup>

All these data have led to the assumption that if oestrogens were implicated in the aetiopathogenesis of the disease, the use of therapies that increased oestrogen levels, either by exogenous addition or by induction of endogenous production, could be dangerous in these patients; consequently, it is advisable to avoid their use.<sup>6</sup> However, under various circumstances, lupus patients may require some of these treatments, so there have recently been several works attempting to study the actual risks that may arise in these cases.

This work seeks to concisely review the existing scientific evidence about the risks of using, in patients with SLE, various therapies involving exogenous oestrogen addition or induction of increased endogenous production of this hormone.

### Oral contraception

As previously noted, the vast majority of lupus patients are young women and, therefore, of childbearing age. However, in many cases, it is necessary to ensure that patients do not become pregnant because of the activity itself and clinical manifestations of the disease or by the treatment being used to control it.

Using barrier methods has usually been recommended to prevent pregnancy, given that it has traditionally been considered that using oral contraceptives with conjugated estrogens may be dangerous. However, barrier methods have a higher failure rate compared with oral contraception. Other methods such as intrauterine devices can also carry risks for these patients with increased susceptibility to infection and who may also be following treatments that enhance this susceptibility, such as corticosteroids and/or immunosuppressive medications.

For all the above reasons, verifying the real risk involved in the use of oral contraceptives in this group of patients is of particular interest. Until recently, there had been no controlled studies on the use of these compounds in lupus patients for fear of possible adverse effects. Some older reports seemed to link the use of these agents with a reactivation or development of the disease.<sup>7–11</sup> However, these publications were isolated case reports that may have been subject to a publication bias by failing to report cases in which, under similar conditions, taking contraceptives did not produce any harmful effects. At present, the oestrogen content of contraceptives is also significantly lower than the ones used in those cases. More recently, three retrospective studies have been published that studied the use of these agents in lupus patients. In one of them, Jungers et al compared the use of combined contraceptives (oestrogen and progestin) versus the use of progestin alone in SLE patients with renal involvement. They found that the patients taking the former presented a higher number of reactivations.<sup>12</sup> In contrast, Julkonen et al found no significant difference when comparing both types of treatment in lupus patients.<sup>13</sup> In that study, two patients developed venous thrombosis (both had antiphospholipid antibodies) and 78% of patients assigned to take progestin discontinued treatment due to intolerance. Lastly, the third study involved a telephone interview of 404 patients in five hospitals to estimate the frequency of contraceptive and HRT use in lupus patients. Among the patients who had taken contraceptives, only 13% reported some type of clinical reactivation (usually mild), which seemed to indicate that these agents were well tolerated. These studies, besides presenting somewhat contradictory results, had various limitations: they were retrospective studies, there were only a small number of patients in the first two studies (the first of them is limited to only patients with lupus nephritis) and the third study was based on telephone interviews, so it may have a significant memory bias.<sup>14</sup>

To provide better evidence on this issue, we developed the clinical trial Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA). This study involved 16 U.S. centres and included patients with stable disease who were randomly administered oral contraceptives or a placebo. Patients with moderate or high levels of antiphospholipid antibodies and/or history of thrombosis were excluded and the development of disease exacerbation was evaluated (classified as mild, moderate or severe). After a year of monitoring, there were no significant differences in the number of any type of clinical reactivations; neither were they observed in regard to the development of thrombotic complications (two episodes in the group treated with contraceptives and three in the placebo group).<sup>15</sup>

Almost simultaneously, the group of Dr. Sánchez-Guerrero published the results of their work, which compared three types of contraception in lupus patients (oral with conjugated oestrogens, oral with only progestins and the use of an intrauterine device). After one year's follow-up, the study showed no differences in clinical activity measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or the number of exacerbations. The authors report only three thrombotic events (all in patients with hormone treatments) and two local infections in women using the intrauterine device.<sup>16</sup>

Together, these results suggest that oral contraceptive use appears to be relatively safe in patients with SLE, at least in patients with stable disease. However, it is not possible to give a clear answer about the potential thrombotic risks, since none of the studies were specifically designed to analyse this. In fact, the SELENA study excluded patients with increased thrombotic risk, and the number of cases with this complication in both studies was insufficient to establish definitive conclusions.

### Hormone replacement therapy

The great preponderance of women with this disease and its relationship to oestrogen makes menopause an *a priori* important factor to be considered in SLE. In fact, it has been speculated that the decline of typical oestrogen levels of this life phase could produce an attenuation of the disease among women in whom the disease had begun before or produce less severe clinical symptoms in lupus patients with a post-menopausal onset.<sup>17,18</sup> A study of Mexican patients showed a moderate decrease in clinical activity when the patients arrived at menopause.<sup>19</sup> However, it has recently been shown that this effect is due more to the natural history of the disease, which tends to present a progressive decline in clinical activity, than to an effect caused by the menopausal state.<sup>20</sup> When lupus patients with a pre- and post-menopausal start were compared longitudinally, it was observed that differences in clinical manifestations (lupus nephritis was more common in patients with pre-menopausal start, while arterial ischemic events were more common in patients with post-menopausal start), in clinical activity or in the cumulative damage were associated with patient age rather than with menopausal status *per se*.<sup>21</sup>

Regardless of the possible influence of menopause on the clinical course of lupus, the fact is that given the levels of survival achieved in this disease, the number of lupus patients of menopausal age with diverse climacteric symptoms and, therefore, HRT subsidiaries will be increasingly larger. This treatment may also have positive effects on bone metabolism in a population that is particularly at risk of osteoporosis due to various factors, including menopause itself, suffering from a chronic inflammatory disease or having been treated with corticosteroids. Against these positive effects would be, once again, the potential for providing exogenous oestrogen to these patients; there are also the possible adverse cardiovascular effects evidenced in the Women's Health Initiative Study,<sup>22</sup> which could be even more evident in these patients due to the risk associated with the

disease itself with respect to the early development of cardiovascular problems.<sup>23–25</sup> However, retrospective studies published several years ago suggest that the use of HRT does not increase the risk of disease exacerbations.<sup>26,27</sup> These results were recently confirmed by prospective studies carried out with a larger number of patients. Thus, the SELENA project also carried out a randomized clinical trial with the same design as previously, but this time comparing HRT and placebo.<sup>28</sup> After one year's follow-up, using HRT was not shown to be associated with an increase in severe SLE exacerbations; however, there was a modest increase in mild and moderate exacerbations. Similarly, results from another clinical trial (HRT vs placebo) performed in Mexico<sup>29</sup> and the experience gained with the LUMINA cohort ("LUPus in MInorities: NAture versus nurture", a multiethnic group prospectively monitored over 14 years)<sup>30</sup> have confirmed the lack of association between the use of HRT and changes in the degree of clinical activity (assessed by various standardised indices) or the frequency of clinical exacerbations.

With respect to the potential risk of suffering atherothrombotic complications, as occurred with the use of contraceptives, both the SELENA study and Dr. Sánchez-Guerrero's group failed to provide conclusive information. This issue was specifically studied in the LUMINA cohort, without any evidence that HRT was associated to venous thrombosis or arterial ischemic events.<sup>31</sup> However, this study once again excluded patients at high risk of thrombosis, so the real risk in this group of patients still remains unclear.

### Assisted fertilisation

The progress observed in recent decades in the management of SLE in general and of pregnancy in lupus patients in particular has led to an improvement in foetal survival in these patients. At present, it is largely similar to that of the general population when the pregnancy takes place in a planned manner. This, in turn, has led to an increase in the number of patients with SLE and infertility problems not arising from this condition who wish to undergo assisted fertilisation techniques.

The only assisted fertilisation technique that can be performed is isolated ovarian stimulation. This process is carried out by hormonal manipulation, seeking follicular maturation to induce ovulation to increase the odds of conception, either by natural means or by artificial insemination. In other cases, egg retrieval and *in vitro* fertilisation are performed after ovarian stimulation, followed by uterine reimplantation of fertilised eggs. Ovarian stimulation may be achieved through different protocols. One possibility is to use anti-oestrogens (usually clomiphene), which act at the hypothalamic level by blocking the negative feedback produced by gonadotrophins at this level. This in turn leads to a peak in gonadotrophin production. Gonadotrophins can be administered directly or their production can be increased by administering analogues of the hormone that stimulates it. The latter agents administered in a sustained manner initially induce a transient stimulation that is followed by a suppression of oestrogen production. This leads to a chemically-induced menopausal state that allows a programmed induction of ovulation through sequential gonadotrophin administration. The main risk derived from the use of gonadotrophins and analogues of the hormone that stimulates gonadotrophin production is ovarian hyperstimulation syndrome. This condition is uncommon but potentially serious as it causes polyserositis by increasing capillary permeability, ovarian oedema, electrolyte alterations, hypotension, hypercoagulability and venous thrombosis.<sup>32</sup>

Regardless of what type of techniques and protocols are used, the end result of these procedures is a temporary increase in oestrogen levels (approximately 10 times more than physiological levels), with the potential risk that this may cause in lupus patients. However, it is also interesting to note that oestrogen levels reached during ovarian

stimulation cycles are, in turn, about ten times lower than those reached in late stages of pregnancy.

There are no prospective studies on the use of these techniques in lupus patients that enable definitive clinical conclusions and recommendations to be established with a view to their use. Some isolated clinical case reports have reported the development of three SLE cases after ovarian stimulation,<sup>33</sup> one fatal case of lupus reactivation following gonadotrophin administration, (the patient presenting polyarthritis and transverse myelitis complicated by pulmonary thromboembolism that ultimately led to death<sup>34</sup>) and the appearance of venous thrombosis after the use of clomiphene.<sup>35</sup> The most extensive experience comes from two retrospective studies on the use of these techniques in patients with SLE. One was a French study that analysed data from 21 patients<sup>36</sup> and the other one described the experience of a New York centre with 19 patients.<sup>37</sup> However, both cases mixed SLE patients with patients suffering from primary antiphospholipid syndrome and asymptomatic patients with some kind of positive serology. Overall, there are data from 20 patients with SLE (three of them diagnosed after completing ovarian stimulation) who were administered a total of 78 cycles of treatment. Clinical reactivations that could be related to SLE were observed in 13 cases (17% of the cycles), although only one of them, consisting in the development of lupus nephritis, could be regarded as serious. Three patients also presented haemolysis, elevated liver enzymes and low platelets syndrome, and it remains questionable whether these cases were merely incidental complications or if they had a relationship with the base lupus disease. Only one case of venous thrombosis was described, in one of the 13 episodes of lupus reactivation. However, it should be noted that most patients described in these studies were on some form of antithrombotic prophylactic treatment (heparin, aspirin or combination therapy) decided empirically, so this information is of little value in establishing the real risk of such complications. Finally, it must also be noted that the French study data suggest that the use of gonadotrophins (in comparison to the use of clomiphene) may be more effective, but also seems to carry a greater risk of exacerbations and thrombotic complications.

### Conclusions

Despite the involvement of oestrogen in the pathogenesis of SLE, the scientific evidence according to published studies suggests that the use of various treatments involving exogenous oestrogens (oral contraceptives and HRT) and the use of agents that induce endogenous oestrogen production (assisted reproduction) seem to be relatively safe. However, it is important to note that the application of these therapies should always be individualised, balancing the benefits and possible risks. All cases in which these treatments are considered must be cases of inactive disease and patients should be monitored with special attention to any problems that may develop. Finally, it should be emphasised that there is insufficient information about the thrombotic risks that these therapies could cause. Special attention must therefore be paid to this problem, especially in patients at high risk for these complications.

### Conflict of interests

The authors declare no conflict of interests.

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