

# The use of sex hormones in women with rheumatological diseases

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A number of rheumatological diseases predominantly affect women of reproductive age. There has always been concern that the use of oestrogen-containing agents such as combined hormonal contraception and hormone therapy might aggravate these conditions. This article reviews the up-to-date evidence regarding the safety of using these agents in women with various rheumatological diseases, with emphasis on systemic lupus erythematosus and rheumatoid arthritis. In the absence of antiphospholipid antibody or other pro-thrombotic risk factors, combined hormonal contraception is not contra-indicated in most rheumatological conditions including inactive systemic lupus erythematosus. Moreover, hormone therapy is generally not contra-indicated except for women with active systemic lupus erythematosus disease where its effect on disease flare is less clear and individual judgement is required.

## Introduction

Many rheumatological diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), polymyositis and dermatomyositis, systemic sclerosis, and Sjögren's syndrome predominantly affect females. A considerable proportion of these patients are of reproductive age. Conceivably, the female predilection for many of these conditions could be because oestrogens play some part in their pathogenesis.<sup>1</sup> It has even been demonstrated that oestrogen can potentiate the phagocytic and antigen-presenting activity of macrophages, promote the maturation of T-helper (T<sub>H</sub>) cells, and activate polyclonal B-cells.<sup>2</sup> Hence, the use of oestrogen-containing compounds such as combined hormonal contraceptives and hormone replacement therapy, or hormone therapy (HT) which is the terminology now preferred, would theoretically aggravate these conditions and raise concerns among doctors taking care of such patients.

For women who have no plans for pregnancy or those whose disease status deems them unfit for pregnancy, a safe and effective contraceptive choice is obviously needed. Owing to the complexity of these disease entities and the limited scientific evidence available in the literature, there have been many myths and controversies among rheumatologists and gynaecologists alike over the use of hormonal contraceptives, especially the combined oestrogen-progestogen preparations. As a result, these women, particularly those suffering from SLE, have often been denied of the use of hormonal contraception, despite the very effective and reversible protection from pregnancy it can provide.

Additionally, women with autoimmune conditions are more prone to premature ovarian failure as a result of their disease or its treatment with cytotoxic agents. Accordingly, they are at risk of developing premature osteoporosis, which may also be related to glucocorticoid use. The use of HT in these circumstances is yet another controversial issue.

The aim of this article was to review the most up-to-date evidence regarding the use of hormonal contraception and HT in patients with rheumatological diseases and provide some guidance in clinical management.

## Methods

A search in PubMed was performed using the terms "contraception" or "contraceptive", "hormone replacement therapy" in combination with "lupus", "rheumatoid arthritis", "polymyositis", "dermatomyositis", "systemic sclerosis" and "Sjögren's syndrome". Systematic reviews and randomised controlled trials published between 1990 and December 2010 were searched and reviewed.

### Key words

Arthritis, rheumatoid; Contraceptives, oral, hormonal; Hormone replacement therapy; Lupus erythematosus, systemic; Rheumatic diseases

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## 性激素於女性風濕患者之使用

不同種類的風濕病多見於生育年齡的女性。一直備受關注的是含有雌激素的複合激素避孕藥及激素治療或會使風濕病的病情惡化。本文探討患有各種風濕病的女性安全使用這些含雌激素藥物的最新證據；討論集中在系統性紅斑狼瘡及類風濕關節炎的疾病。在沒有抗磷脂抗體及其他血栓風險因素的情況下，大多數風濕病患者（包括非活躍期系統性紅斑狼瘡）對於服用複合激素避孕藥並無禁忌反應。一般來說，除了活躍期系統性紅斑狼瘡患者，激素治療對於患有風濕病的女性並無禁忌反應。對於活躍期系統性紅斑狼瘡患者來說，至今仍未確定激素治療會否引致病情惡化，所以需按個別情況作出判斷。

### Systemic lupus erythematosus

Systemic lupus erythematosus is more prevalent in females than males with a ratio of approximately 9:1. It is one of the most common rheumatological diseases affecting women of reproductive age, for which the use of sex steroids poses a concern.<sup>1</sup> Oestrogen and pregnancy shifts the balance of  $T_H1$ / $T_H2$  cytokine production towards the latter, and as SLE is predominantly a  $T_H2$  cytokine-mediated condition, theoretically it is prone to aggravation if tissues have high oestrogen content.<sup>2</sup>

In women who consider using oestrogen-containing compounds, an important consideration is the presence of antiphospholipid antibodies (APL Abs). Antiphospholipid antibodies, including lupus anticoagulant and anticardiolipin antibody, are commonly found among patients with autoimmune diseases, particularly SLE. Women who are positive for APL Abs are prone to both arterial and venous thromboembolism (VTE), and oestrogen-containing contraceptives and HT are therefore contra-indicated in these women.

### Hormonal contraception

Large case-control studies suggested that current but not past use of combined oral contraceptives (COC) is associated with an increased incidence of SLE.<sup>3,4</sup> The risk appeared higher in those using second-generation and high-dose pills.<sup>4</sup> A recently published systematic review on the use of hormonal contraception in SLE assessed 13 studies,<sup>5</sup> including two good-quality randomised controlled trials (RCTs).<sup>6,7</sup> This incorporated all currently published clinical trials relevant to this topic, and its main findings are summarised as follows.

### Disease activity

The two available randomised trials<sup>6,7</sup> indicated that the use of COC did not lead to increased flares of disease or worsening activity in women with inactive

or stably active SLE. Nor did use of progestogen-only pills (POP) lead to increased disease activity.

### Thromboembolic risk

For patients who are APL Ab-positive, the use of COC adds to the risk of both arterial and VTE<sup>5,8</sup> and is not recommended. For those without such antibodies, there is no adequate good-quality evidence. One RCT<sup>7</sup> reported four VTE events out of 162 women, two of whom used COC and the other two used POP, versus none in those using an intrauterine contraceptive device. However, all the four patients were APL Ab-positive. Another RCT<sup>6</sup> reported five VTE events out of 183 women with SLE, two using COC and three using placebo, but the APL Ab status of these subjects was unknown. A potential bias with these studies was that women at very high risk of VTE were probably already excluded from the studies, and hence the results may not be applicable to all SLE patients.

### Musculoskeletal complications

One RCT<sup>9</sup> revealed that COC use reduced the risk of musculoskeletal problems (eg muscular atrophy or weakness, deforming arthritis, osteoporosis, vertebral collapse or fracture, avascular necrosis, osteomyelitis and ruptured tendon). Another retrospective analysis<sup>10</sup> of 702 SLE patients showed that ever users of COC (type of COC not specified) had a significantly lower fracture risk compared with never users (53% vs 64%).

### Recommendations

Based on the available results from these studies, the World Health Organization (WHO) has recently added the guidance on the use of contraceptive methods in SLE in the updated medical eligibility criteria (Table<sup>11</sup>). In summary, use of any form of hormonal contraception is not contra-indicated in women with inactive or stably active SLE, with the exception of those whose APL Ab status is positive (or unknown). In the latter condition, combined hormonal contraception in any form is absolutely contra-indicated (WHO 4), and the use of progestogen-only contraception is relatively contra-indicated (WHO 3). Meanwhile, women with SLE may have other co-existing cardiovascular risk factors that also need to be taken into consideration and checked with the WHO guideline,<sup>11</sup> when deciding on the individual's medical eligibility for using hormonal contraception.

### Hormone therapy

The interaction between HT and SLE is another difficult area. Two prospective studies have reported a significant increase in the incidence of new disease

TABLE. Medical eligibility criteria for contraceptive use in patients with systemic lupus erythematosus\*<sup>11</sup>

Condition	Categories of medical eligibility criteria <sup>†</sup>								
	COC, patch, ring	CIC	POP	Progestogen-only injectables		Implants	Copper IUCD		Levonorgestrel intrauterine system
				I	C		I	C	
Positive (or unknown) antiphospholipid antibodies	4	4	3	3	3	3	1	1	3
Severe thrombocytopaenia	2	2	2	3	2	2	3 <sup>‡</sup>	2 <sup>‡</sup>	2 <sup>‡</sup>
Immunosuppressive treatment	2	2	2	2	2	2	2	1	2
None of the above	2	2	2	2	2	2	1	1	2

\* COC denotes combined oral contraceptives, CIC combined injectable contraceptives, POP progestogen-only pills, IUCD intrauterine contraceptive device, I initiation, and C continuation

<sup>†</sup> Categories: 1 = no restriction for the use of the method; 2 = the advantages of using the method generally outweigh the theoretical or proven risks; 3 = the theoretical or proven risks usually outweigh the advantages of using the method (ie relatively contra-indicated); 4 = unacceptable health risk if the method is used (ie absolutely contra-indicated)

<sup>‡</sup> Severe thrombocytopaenia increases the risk of bleeding. The category should be assessed according to the severity of thrombocytopaenia and its clinical manifestations. In women with very severe thrombocytopaenia who are at risk for spontaneous bleeding, consultation with a specialist and certain pre-treatments may be warranted

in HT users, and the risk increased with increasing duration of use.<sup>12</sup> However, some retrospective studies suggested no increase in clinical flares.<sup>12</sup> These issues have been the subject of review.<sup>12</sup>

The best evidence was from the double-blind RCT with the acronym SELENA (Safety of Estrogens in Lupus Erythematosus, National Assessment) trial.<sup>13</sup> It investigated 351 women with inactive disease, who started combined cyclical HT or placebo. The women were APL Ab–negative and had no history of VTEs. There was no difference in the risk of severe flares between the respective groups (7.5% vs 4.5%; odds ratio [OR]=1.75; 95% confidence interval [CI], 0.73-4.22), whereas there was a small increase in risk of mild-to-moderate flares (OR=1.34; 95% CI, 1.07-1.66). A few cases of arterial and venous thrombotic events including one death, three deep venous thromboses (DVTs), one stroke, and one arteriovenous graft thrombosis were reported in the HT group, as well as one DVT in the placebo group. The dropout rate in the study was high, and the overall evidence was inconclusive. Although the evidence seemed reassuring for severe flares, the risk of milder flares and VTEs was less clear. Moreover, in view of the trial’s exclusion criteria, the results were not applicable to women with active disease or at high thrombotic risk. Some other smaller studies did not show any increased risk of SLE flares with HT use.<sup>14-17</sup>

One case-control study included women who were APL Ab–positive.<sup>18</sup> No difference in incidence or timing for the development of coronary heart disease (CHD) was found between the 114 HT users and 227 non-users. Multivariate analysis revealed that age, but not HT use, was associated with CHD development.

With regard to other compounds related to HT, a recent small RCT of 30 women with inactive or stable SLE suggested that the use of tibolone did not increase flares compared to placebo.<sup>19</sup> A small RCT<sup>20</sup>

among 16 women with SLE taking raloxifene versus 17 taking on placebo revealed no significant difference in disease activity when followed up to 1 year, and there was no VTE. There are currently no safety data on the use of androgens in women with connective tissue diseases. Theoretically, testosterone may be aromatised to oestrogen, and hence its use is not recommended until more data are available.

**Recommendations**

In general, the use of HT should be tailored to individual risks and benefits with reference to the SLE disease activity profile and symptomatology. The main indication of HT should be severe climacteric symptoms impairing quality of life. Hormone therapy can be used when SLE is inactive with no flares for several years, and in women who are APL Ab–negative and not on high-dose steroids. For such women, low-dose transdermal oestrogen combined with a natural progesterone preparation is preferred as it is less thrombogenic.<sup>21</sup> Similarly, it has been suggested that micronised progesterone or pregnane derivatives did not result in increased thromboembolic risk, whereas norpregnane derivatives were associated with a 4-fold increase in VTE risk.<sup>22</sup>

For those with mildly active disease, a non-oestrogenic agent (eg antidepressant or progestogen) is the preferred first-line treatment. If this is not effective, low-dose transdermal HT can be used with close monitoring of disease activity. For those with severe active disease or who are APL Ab–positive, HT should be avoided. The use of HT in those with premature ovarian failure should generally be beneficial and is recommended.

**Rheumatoid arthritis**

Rheumatoid arthritis occurs 2 to 3 times more commonly in women than in men. Disease severity

tends to diminish during pregnancy and hence there is some suggestion of hormone dependence. As RA is a  $T_H1$  cytokine-mediated condition, high oestrogen exposure should theoretically ameliorate disease activity.<sup>2</sup>

### Hormonal contraception

There is some evidence that past users of COC have a lower incidence of RA, whereas other reports suggest no such protective effect.<sup>23</sup> A recent systematic review on the safety of hormonal contraceptives in women suffering from RA included only six relevant articles.<sup>24</sup> All available data were on the COC pill. The only fair-quality prospective cohort study in 112 women with RA showed a trend towards improvement in both objective and subjective measures of RA symptoms, but was underpowered and the result did not reach statistical significance. The other five poor-quality studies showed either little or no effect of COC use on disease progression.

### Recommendations

As the current limited evidence does not suggest any adverse effect of COC use on disease progression, there should be no contra-indication in RA patients. There are currently no data on the use of other forms of hormonal contraceptives in women with RA. Women with RA are more prone to osteoporosis either due to the disease activity or use of systemic steroids. There is an established association between a reversible decrease in bone mineral density (BMD) and the use of depot medroxyprogesterone acetate.<sup>25</sup> Its clinical significance in RA patients is uncertain however. Individualised clinical judgement should be exercised.

### Hormone therapy

According to one RCT involving 88 postmenopausal women, using HT significantly ameliorated symptoms, disease activity scores and radiological disease progression, and improved BMD.<sup>26</sup> Another four RCTs did not confirm any statistically significant difference in symptom severity in HT users versus non-users, although in one of the studies there was significant improvement in symptoms after women with poor compliance were excluded.<sup>27-30</sup>

### Recommendations

As the use of HT in women with RA was not shown to aggravate disease activity, and there was some suggestion of improvement, HT is not contra-indicated when treatment appears necessary. There has not been adequate evidence on the use of HT in postmenopausal women with RA for specific prophylaxis against osteoporosis.

## Other rheumatological conditions

There are currently no clinical safety data on the use of hormonal contraception and HT in other rheumatological conditions such as dermatomyositis, Sjögren's syndrome and systemic sclerosis, which also occur more commonly in women of reproductive age. As these diseases are not generally oestrogen-related, the use of sex steroids in affected women is probably safe, provided any co-existing hypercoagulable state or other contra-indications are absent. Antiphospholipid antibodies are commonly found in various autoimmune diseases and should be ruled out before exogenous sex steroids can be safely prescribed. In women with Raynaud's phenomenon, oestrogen has been found to have a vasodilator effect and may improve symptoms.<sup>31</sup> Patients using long-term glucocorticoids are prone to osteoporosis. There is some suggestion that HT use improves BMD in glucocorticoid users, although the effect on fracture prevention is unclear.<sup>32</sup> Bisphosphonates are generally considered to be the evidence-based first-line option for the prevention and treatment of glucocorticoid-induced osteoporosis, but in hypoestrogenic women with climacteric symptoms, HT can be considered.<sup>32</sup>

## Conclusion

Women with rheumatological conditions have the same needs for safe and effective contraceptive choices as the general population. Clinicians should fully understand the advantages and drawbacks of each contraceptive method, the effect of the different methods on disease activity and other health risks, the possibility of interactions with concurrent medications, and the needs and preferences of the couple. Combined hormonal contraception is effective, convenient, and reversible. It is not contra-indicated in most autoimmune conditions including inactive SLE in the absence of APL Abs or other pro-thrombotic risk factors. For women in whom the use of oestrogen is a concern, progestogen-only methods can be considered, except that BMD loss associated with progestogen-only injectables impose some concern in women with a co-existing predisposition to osteoporosis. For women who need HT, it is generally not contra-indicated except in those with active SLE disease for whom physicians must exercise individual judgement. Nonetheless, the guiding principles in prescribing hormonal contraceptives and HT for the general population should also apply to women with rheumatological conditions. They should always be reviewed in the context of co-existing medical conditions and other risk factors which favour or contra-indicate the use of hormonal agents. By this means, the balance between benefits and risks can be properly assessed and compared against all other available alternative treatment options.

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