RISKS OF OVULATION-INDUCTION THERAPY IN SYSTEMIC LUPUS ERYTHEMATOSUS

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SUMMARY

We report on four women with systemic lupus erythematosus who developed two types of complications after ovulation-induction therapy for primary or secondary infertility. Primary infertility was associated with endometriosis in one patient. Three had previously known systemic lupus erythematosus. All had inactive disease at onset of ovulation-induction therapy. Three patients developed symptoms consistent with moderate lupus flare a few weeks after the onset of ovulation-induction therapy. One patient developed inferior vena cava and unilateral left renal vein thrombosis. No patient became pregnant. A high oestrogen level induced by ovulation-induction therapy may explain the occurrence of lupus flare in patients with prior inactive lupus. All our patients had prior asymptomatic antiphospholipid antibodies. One patient developed a major thrombotic event. The presence of antiphospholipid antibodies increases the thrombotic risk related to ovulation-induction therapy. We conclude that ovulation-induction therapy should be restricted to patients with long-standing inactive systemic lupus erythematosus. A preventive increase of the corticosteroid dosage should be proposed in addition to heparin or antiaggregant therapy for those with prior asymptomatic antiphospholipid antibodies, or with heparin therapy for those with prior antiphospholipid antibody-related events.

KEY WORDS: Systemic lupus erythematosus, Antiphospholipid syndrome, Ovulation-induction therapy, Thrombophlebitis.

THE importance of oestrogen in the pathogenesis of systemic lupus erythematosus (SLE) is well known [1, 2]. The latter decade has been characterized by an improvement in SLE prognosis and better management of SLE pregnancy. These facts led to an increased number of pregnancies and incited treatment of infertility. Several regimens are used for ovulation induction. All stimulate follicular development and increase oestrogen serum levels [3]. Oestrogen also increases the risk of thrombophlebitis [4]. Hence, it would be considered that ovulation-induction therapy (OIT) may exacerbate or induce SLE in predisposed women, or favour thrombotic events in the case of antiphospholipid antibodies (aPL) [5]. We describe four cases of SLE who developed OIT-related complications.

CASE REPORTS

Case 1

A 24-yr-old Malayan woman presented in 1988 with discoid lupus, photosensitivity, alopecia and antinuclear antibodies (ANA) at the level of 1/50e. She had a history of elective abortion for unwanted pregnancy in 1979. In 1990, she complained of more than 4 yr infertility. Before OIT was started, she was referred to our department. She had only mild arthralgia and a discoid lesion. Laboratory tests showed rheumatoid factor, anticardiolipin (aCL) antibodies (25 GPL units) and biologic false-positive serologic tests for syphilis. Aspirin 100 mg daily was started. Three cycles of OIT [triptoreline, purified follicle-stimulating hormone (FSH) and human menopausal gonadotrophin (hMG)] with in vitro fertilization and embryo transfer (IVFET) were performed in May and October 1990, and January 1991. A few days after the latter cycle onset, she developed malar rash, skin vasculitis, alopecia and polyarthritis. Laboratory tests showed ANA (1/200e), anti-Sm antibodies, rheumatoid factor and aCL (31 GPL units), with no anti-dsDNA antibodies and lupus anticoagulant (LA), and normal serum complement level. She recovered rapidly under 80 mg/day prednisone.

Case 2

A 26-yr-old Zairian woman presented in 1982 with fever, polyarthritus, myalgias, splenomegaly and pulmonary infiltrates. She recovered under prednisolone, but a relapse occurred 1 yr later. At that time, pelvic endometriosis was discovered. Its recurrence under danazol required left salpingo-oophorectomy in 1986. As she had complained of 3 yr infertility, she underwent two cycles of OIT (leuproleline, hMG) with IVFET in 1991, and three others in February 1992, June 1992 and March 1993. A relapse sensitive to prednisolone occurred during this period. Corticosteroids were stopped in January 1994. One month later, 10 days after the onset of a fifth cycle of OIT, she complained of chest pain and exertion dyspnoea. She was then referred to our institution. She admitted having intentionally masked her lupus history to gynaecologists. Chest X-ray showed recurrence of pulmonary infiltrates. ECG displayed abnormal repolarization consistent with pericarditis. Laboratory tests showed leucocyte count 2900/mm³, low C3 complement level, positive ANA, anti-dsDNA and aCL (35 GPL units).

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Case 3
A 20-yr-old French woman presented in January 1985 with polyarthritis, skin lesions and recurrent episodes of lip and skin oedema sensitive to corticosteroids. In July 1993, she complained of a 3 yr infertility. At that time, she had transient polyarthalgias, ANA (1/100e) with anti-dsDNA, aCL (96 GPL units) antibodies, LA and a low serum complement level. In July 1994, she underwent a first cycle of OIT (leuprolene, hMG) with IVFET under hydroxychloroquine and 20 mg/day prednisone. Three weeks later, polyarthritis and lip oedema recurred with no pregnancy. All symptoms resolved under a transient increased prednisone dose to 30 mg/day. A second cycle of OIT was performed in December 1994 after a systematically increased dose of prednisone from 20 to 30 mg/day. No SLE flare or pregnancy occurred.

Case 4
A 24-yr-old West Indian woman presented in October 1991 with fever, polyarthritis, myalgias, dysphagia, Raynaud's phenomenon and swollen hands. Laboratory tests showed rheumatoid factor, aCL (98 GPL units), haemolytic anaemia, ANA with anti-RNP antibodies. Symptoms remitted under prednisone 40 mg/day, but recurrent when the dose was reduced to 20 mg/day. Addition of high-dose i.v. immunoglobulins and azathioprine was ineffective. Methotrexate (7.5 mg weekly) was started in November 1993. The prednisone dose was then gradually reduced to 8 mg/day. In August 1994, she stopped methotrexate by herself. Three months later, as she had complained of a 2 yr infertility, she underwent a first cycle of OIT (hMG). Two weeks later, and during a febrile bacterial pneumonia, she developed inferior vena cava and left renal vein thrombosis. Laboratory tests showed positive ANA, anti-dsDNA and aCL (100 GPL units, 86 MPL units) antibodies and a low serum complement level. In remission on 8 mg/day prednisolone (60 mg/day) was restarted with rapid improvement. No pregnancy occurred.

Prior to OIT, patient 1 had discoid lupus, and patients 2 and 3 SLE. The fourth patient had a mixed connective tissue disease [6] with features of SLE. The data are summarized in Table I. All patients fulfilled at least four ARA criteria for SLE [7]. Primary infertility was associated with endometriosis in patient 2. Patients with endometriosis have a higher risk of developing SLE [8]. These four patients exhibited two types of complications after OIT. Patients 1, 2 and 3 developed a moderate SLE flare a few weeks after OIT onset. Ben-Chetrit and Ben-Chetrit [9] recently reported on two women with primary or secondary infertility and no prior SLE who developed SLE flare after OIT. The influence of sex hormones in SLE is well known. In New Zealand Black/New Zealand White F1 mice, females develop nephritis more rapidly and die earlier than males. The course of prepubertal castrated males is similar to that of females. Androgen-treated females have a longer survival than those non-treated [10, 11]. In humans, the deleterious effect of endogenous or exogenous oestrogen is suggested by the predominance of SLE in women of child-bearing age, SLE exacerbation during pregnancy [2, 12, 13], following oestrogen-containing contraceptive therapy [1] and a higher SLE rate in oestrogen replacement-treated women [14]. Despite anecdotal reports [15], the incidence of SLE is not increased in Klinefelter's syndrome [16]. On the contrary, SLE seems to improve under antigonadotrophic drugs [17] and gonadotrophin-releasing hormone analogues [18] that down-regulate gonadotrophin secretion.

OIT is based on a combination of various regimens. Ovarian follicular development can be obtained by clomiphene administration which increases gonadotrophin-releasing hormone production, or by gonadotrophin-releasing hormone administration that enhances endogenous FSH and luteinizing hormone (LH) production, or by hMG or purified FSH administration that directly stimulates follicles. Human chorionic gonadotrophin (hCG) injection then induces ovulation. Whatever the method used, an exponential

**TABLE I**

<table>
<thead>
<tr>
<th>Age, ethnic origin and duration of infertility</th>
<th>Diagnosis prior to OIT</th>
<th>Anti-phospholipid antibodies</th>
<th>Other serological data</th>
<th>Status prior to OIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 yr Malayan 4 yr secondary infertility</td>
<td>Discoid lupus</td>
<td>aCL 25 GPLU</td>
<td>Negative ANA</td>
<td>Discoid lupus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No LA</td>
<td>Negative DNA</td>
<td>No therapy</td>
</tr>
<tr>
<td>26 yr Zairian 3 yr primary infertility</td>
<td>SLE</td>
<td>aCL ND</td>
<td>Positive ANA</td>
<td>In remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No LA</td>
<td>Positive DNA</td>
<td>No therapy</td>
</tr>
<tr>
<td>20 yr French 3 yr primary infertility</td>
<td>SLE</td>
<td>aCL 96 GPLU</td>
<td>Positive ANA</td>
<td>In remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LA present</td>
<td>Positive DNA</td>
<td>On 20 mg/day P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low complement</td>
<td>200 mg/day HC</td>
</tr>
<tr>
<td>24 yr West Indian 3 yr primary infertility</td>
<td>Mixed connective tissue disease</td>
<td>aCL 98 GPLU</td>
<td>Positive ANA</td>
<td>In remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No LA</td>
<td>Negative DNA</td>
<td>On 8 mg/day P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low complement</td>
<td></td>
</tr>
</tbody>
</table>

ANA, antinuclear antibodies; DNA, anti-dsDNA antibodies; aCL, anticardiolipin antibodies; ND, not done; LA, lupus anticoagulant; P, prednisone; HC, hydroxychloroquine.
rise in the serum oestradiol level is observed [3, 19]. It should be noted that none of our patients became pregnant. High OIT-induced oestrogen levels may explain SLE flare in patients with a predisposition to SLE or previously inactive SLE. A prior systematically increased prednisone dose may successfully prevent OIT-related flare, as in case 3. It may also increase the rate of successful pregnancy as a low complement level predicts fetal loss [12, 13].

Patient 4 had previous asymptomatic aPL and developed extensive thrombophlebitis coinciding with pneumonia. Oestrogens increase the risk of thrombophlebitis [4, 20]. Thrombotic events following ovarian stimulation without ovarian stimulation syndrome have been reported [21]. Certain infections have been incriminated as predisposing to thrombophlebitis, but the role of infection per se or the concomitant immobilization is difficult to explain [20]. The thrombotic risk related to aPL is estimated to range from 11 to 100% [5]. It should be noted that all our four patients had aPL. The prevalence of aPL is 30–40% in SLE [5]. A deleterious effect of aPL in the implantation of embryo has been demonstrated in animal models [22]. The question of a possible aPL-induced infertility in women is asked, and requires further studies. Combination of heparin and aspirin increases the viable pregnancy rate after OIT and IVFET in women with aPL compared with non-treated aPL-positive women [23].

CONCLUSIONS

Our study, although not case controlled, suggests that OIT per se may trigger disease activity in patients with SLE. Should OIT be discouraged in such patients, due to the consequential huge increase in oestrogen levels? The answer is probably no, considering that such an increase remains far below that accompanying pregnancy. However, this procedure should be restricted to patients with long-standing inactive SLE [2, 18, 19]. A preventive moderate increased corticosteroid dosage should be proposed to patients receiving OIT, in addition to heparin or antiaggregant therapy for those with prior asymptomatic aPL antibodies, or with heparin therapy for those with prior aPL-related thrombotic events.

REFERENCES