CASE REPORT

Treatment of autoimmune premature ovarian failure

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Introduction

To restore fertility effectively for a young woman with autoimmune premature ovarian failure, the clinician needs first, a sensitive and specific non-invasive method to confirm that indeed the woman has ovarian failure on an autoimmune basis, and second, a treatment to administer that has been proven safe and effective by prospective randomized controlled trial.

At present, the clinician has neither of these (Nelson et al., 1996; Wheatcroft et al., 1997). This makes autoimmune ovarian failure a frustrating condition for the young couples that it robs of fertility, and a frustrating condition for the clinicians that are caring for them. This frustration may lead to the use of empirical treatments, with which the potential benefits and risks are poorly defined. To bring focus to this issue, we present here two cases of young women with premature ovarian failure who were treated with glucocorticoids in the hopes of restoring fertility. The first case illustrates the potential benefit of such therapy, and the second case illustrates a potential risk.

Autoimmunity is a well established mechanism of ovarian failure (Irvine et al., 1968; Sedmak et al., 1987; Bannatyne et al., 1990) and, as a group, patients with karyotypically normal premature ovarian failure are known to have increased peripheral T lymphocyte activation (Rabinowe et al., 1986; Nelson et al., 1991). On the other hand, simple elevated follicle stimulating hormone has been shown to be associated with increased peripheral T lymphocyte activation (Hoeck et al., 1995). Nevertheless, increased numbers of activated peripheral T lymphocytes has been described in other autoimmune endocrine disorders, such as recent onset Grave’s disease (Jackson et al., 1984), insulin dependent diabetes mellitus (Jackson et al., 1982) and Addison’s disease (Rabinowe et al., 1984).

One percent of women by age 40 years spontaneously develop premature ovarian failure (Coulam et al., 1986), a condition characterized byamenorrhea, infertility, sex steroid deficiency, and elevated serum gonadotrophin concentrations (Rebar and Cedars, 1992; Nelson et al., 1996). Anecdotal reports have suggested that glucocorticoid treatment may be useful in treating autoimmune premature ovarian failure (Cowchock et al., 1988; Taylor et al., 1989; Luborsky et al., 1990; Blumenfeld et al., 1993; Corenblum et al., 1993).

Case reports

Case 1

A 26-year-old woman (gravida 2, para 1, abortus 1) presented to her private physician with acute abdominal pain and a right adnexal mass. At surgery, a 7 cm multiloculated cystic structure was removed from the right ovary. Histological examination revealed luteinized follicle cysts with dense lymphocytic infiltration. At age 28 years, the patient was referred to the National Institutes of Health Clinical Center.

Review of the slides showing the pathology confirmed the...
diagnosis of lymphocytic oophoritis. Immunohistochemistry utilizing immunoperoxidase staining was used to characterize the nature of the lymphocytic infiltration. The infiltration consisted of T-cells, plasma cells and scattered aggregates of B-cells (Figure 1).

The patient had experienced menarche at age 10 years and had developed secondary sex characteristics appropriately. Her menses were regular every 28 days until she became pregnant at age 23 years. After the delivery of her only child she began taking oral contraceptives and became pregnant again at age 27 years while using this method. This pregnancy resulted in a spontaneous abortion and thereafter her menstrual cycles became irregular. Five months later the patient underwent emergency ovarian surgery. She subsequently developed amenorrhea and experienced symptoms of sex steroid deficiency (hot flashes, vaginal dryness, and dyspareunia). Her serum gonadotrophin concentrations were found to be elevated [follicle stimulating hormone (FSH) 40 mIU/ml and luteinizing hormone (LH) 65 mIU/ml].

At age 29 years, she participated in a National Institute of Child Health and Human Development randomized, prospective, placebo-controlled trial of alternate-day prednisone for treatment of patients with histologically confirmed autoimmune ovarian failure. The protocol was approved by the National Institute of Child Health and Human Development Institutional Review Board. She received alternate day prednisone therapy for 16 weeks (mean daily dose of 11 mg, total cumulative dose of 1225 mg). During the prednisone treatment the patient resumed spontaneous menstrual bleeding six times and had ovulatory progesterone concentrations (>9.5 nmol/l) on four occasions. Her serum gonadotrophin concentrations decreased (Table I). Subsequently, the Pharmacy Department informed us that the patient had been randomized to take the active drug.

Case 2
A 36-year-old nulligravida woman presented to her private physician complaining of infertility. Pertinent findings included vasomotor symptoms, amenorrhea and elevated serum gonadotrophin concentrations. She had experienced menarche at age 13 years and had developed secondary sex characteristics appropriately; she had had regular 28 day menstrual cycles until age 34 years, when she began skipping menses. Her past medical history was significant for Hashimoto’s thyroiditis (Weetman and McGregor, 1994). With a presumptive but unconfirmed diagnosis of autoimmune premature ovarian failure, her private physician empirically prescribed a course of
Autoimmune premature ovarian failure

<table>
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<tr>
<th>Week</th>
<th>Dose alternate-day prednisone (mg/day)</th>
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<td>FSH (mIU/ml)</td>
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*Sample not drawn.

Discussion

Autoimmune premature ovarian failure is a frustrating disorder for patients and their physicians. To date there is no accurate serum marker available to identify patients who have premature ovarian failure due to autoimmunity (Wheatcroft et al., 1997) and the specific antigen involved in the development of autoimmune premature ovarian failure has yet to be discovered. Autoimmune diseases are characterized by the presence of histological inflammatory features, other coexisting autoimmune disorders, and circulating organ-specific autoantibodies (Pekonen et al., 1986; Muir and MacLaren, 1991; Hoek et al., 1997). There is evidence suggesting the presence of ovarian antibodies in the sera of patients with premature ovarian failure (Coulam and Ryan, 1979).

Ovarian biopsy is currently the only way to diagnose autoimmune premature ovarian failure with certainty. Nevertheless, there is no treatment proven effective by prospective, randomized, controlled study to restore fertility for these patients. Therefore, ovarian biopsy outside a controlled trial is not clinically indicated (Khastgir et al., 1994; Nelson et al., 1996).

Young women with premature ovarian failure have intermittent ovarian follicle function (Rebar and Cedars, 1992; Nelson et al., 1994) and nearly 20% of these women ovulate spontaneously during 4 months of observation (Nelson et al., 1994). Spontaneous pregnancies have occurred after the diagnosis of premature ovarian failure (Polansky and DePapp, 1976; Shangold et al., 1977; Szlachter et al., 1979; Aiman and Smentek, 1985; Ohswa et al., 1985; Alper et al., 1986; Kreiner et al., 1988) and we have had patients who have ovulated after placebo treatment (Nelson et al., 1996). Although autoimmune lymphocytic oophoritis is a known cause of premature ovarian failure, it is not known what proportion of women with premature ovarian failure develop the condition on an autoimmune basis. Indirect immunofluorescence using various sources of ovarian tissue (Damewood et al., 1986; Ho et al., 1988) and enzyme-linked immunosorbent assay (ELISA) (Luborsky et al., 1990; Gobert et al., 1992; Wheatcroft et al., 1994; Fenichel et al., 1997; Wheatcroft et al., 1997) have been the most commonly used techniques to identify ovarian antibodies. The two methods used for the detection of ovarian
antibodies, indirect immunofluorescence and ELISA, were compared, and neither was found to be reliable (Wheatcroft et al., 1997). Also, using ELISA, it was found that these antibodies are frequently detected in Turner’s syndrome and iatrogenic ovarian failure as well (Wheatcroft et al., 1994). Furthermore, ovarian antibodies detected by this method are non-specific, as they cross-react with other antigens such as those in the Fallopian tube (Wheatcroft et al., 1994). In addition, immunoblotting studies failed to reveal a consistent pattern of binding using the sera of patients with premature ovarian failure on two antigen preparations (Wheatcroft et al., 1997).

Steroid cell antibodies have been identified in patients with premature ovarian failure associated with Addison’s disease (Elder et al., 1981; Uibo et al., 1994; Winqvist et al., 1995). Nevertheless, steroid cell antibodies are not usually present in patients with isolated premature ovarian failure (Betterle et al., 1993; Weetman, 1995; Chen et al., 1996).

Antibodies against membrane-bound receptors are known to cause diseases, such as myasthenia gravis (Lindstrom et al., 1976) and autoimmune hypothyroidism (Drexhage et al., 1981). In addition, anti-FSH receptor antibodies, detected using animal systems, have been reported in a few patients with premature ovarian failure. We have found that immunoglobulin G (IgG) from patients with premature ovarian failure does not interfere with either the FSH-receptor or the LH-receptor interaction, using a recombinant system expressing human FSH and LH receptors (Anasti et al., 1995).

Autoimmune lymphocytic oophoritis is characterized by a selective attack against only developing follicles with sparing of primordial follicles (Irvine et al., 1968; Sedmak et al., 1987; Bannatnye et al., 1990). In most cases follicle development progresses to the Graafian stage. Autoimmune lymphocytic oophoritis sometimes presents with markedly enlarged ovaries containing luteinized cysts, as illustrated by the first case and as previously reported (Rabinowe et al., 1986).

The defect in immune regulation that leads to autoimmune premature ovarian failure is not understood. Although most autoimmune diseases, such as multiple sclerosis, diabetes, and rheumatoid arthritis, appear to be T helper 1 (Th1) cell mediated, experimental data suggests that some autoimmune diseases, such as murine autoimmune post-thymectomy oophoritis and murine autoimmune encephalomyelitis, may be Th2 cell mediated (Lafaille et al., 1997; Maity et al., 1997). The recent identification of a single gene defect on chromosome 21q22.3 causing autoimmune polyglandular failure type 1 (Nagamine et al., 1997; The Finnish–German APECED Consortium, 1997), which in many cases includes autoimmune ovarian failure, may provide a basis for gaining insight into immune regulation and organ specific autoimmunity.

Anecdotal reports have suggested that glucocorticoid treatment may restore ovarian function in women with premature ovarian failure (Cowchock et al., 1988; Taylor et al., 1989; Luborsky et al., 1990; Blumenfeld et al., 1993; Corenblum et al., 1993). There are presently no controlled studies, however, to tell us what proportion of women with autoimmune premature ovarian failure will ovulate in response to immune modulation therapy. More importantly, there are presently no controlled studies to tell us what proportion of women with autoimmune premature ovarian failure will have major com-
plications in response to treatment with glucocorticoids. Gluco-
corticoid administration is the most frequent cause of osteonecrosis of the hip or knee (Mankin, 1992). Pain is usu-
ally the presenting symptom of osteonecrosis, and the pain
exacerbates with the use of the joint. The condition may be
debilitating and require prosthetic hip or knee replacement
(Mankin, 1992). In fact, osteonecrosis accounts for ~50 000
joint replacements performed annually in the USA (Mankin,
1992). Iatrogenic Cushing syndrome is also a well-known
major sequela of chronic corticosteroid administration (Zizic
et al., 1985).

The efficacy of treatment modalities should be documented
by randomized controlled trials (Grimes, 1995). A prospective
randomized controlled study of alternate day prednisone
therapy for autoimmune premature ovarian failure is now
underway at the Clinical Center of the National Institutes of
Health. This study will provide evidence for management
decisions regarding patients with suspected autoimmune pre-
mature ovarian failure. In this study, since there is no diagnostic
serum marker available, histological confirmation of the disease
is a prerequisite for prednisone administration. We performed
an ovarian biopsy when an antral follicle was detected on
ultrasound in six patients with karyotypically normal spontane-
ous premature ovarian failure (Nelson et al., 1994). Interest-
tingly, we found no autoimmune oophoritis in any of these
specimens (Nelson et al., 1994).

The patient (case 1) presented in this case report did have
histologically proven autoimmune oophoritis. While taking
low-dose alternate day glucocorticoid treatment she had had
return of menstrual bleeding six times and ovulatory progester-
one concentrations four times over the 16 week period.
Autoimmune premature ovarian failure is not a life threaten-
ing condition, so aggressive immunosuppression with glucocorti-
coids is not indicated. We developed our alternate day regimen
dose with the objective of giving a dose that might have a
beneficial effect yet be very unlikely to harm anyone. This
strategy would make the studies ethical and worthwhile.

Identifying patients with autoimmune premature ovarian
failure presents the opportunity to restore ovarian function by
treating these patients with the proper immune modulation
therapy. On the other hand, potent immune modulation therapy
can have major complications. In our opinion, there is no role
for empirical corticosteroid treatment of this disorder. There
is need for an international collaborative research effort to make
progress in this condition. In our view, immunosuppression by
corticosteroids for the treatment of premature ovarian failure
should be limited to patients with proven autoimmune oophori-
tis who are participating in placebo-controlled trials designed
to determine safety and efficacy.

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