Premature Ovarian Failure: Is there a role for steroids? A randomized, double-blind, placebo-controlled trial.

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A. Study Purpose and Rationale

Premature ovarian failure is a condition causing amenorrhea, infertility and symptoms compatible with a low estrogen state. It affects approximately 1/100 women under the age of 40 and 1/1000 women under 30 (Anasti et al.) Premature ovarian failure causes anywhere from 4-18% of cases of secondary amenorrhea. The natural history of the disease is that 20-25% of patients, on average, will spontaneously ovulate during 1-5 year period of ovulation. The current standard of treatment is HRT for symptomatic relief fertility treatment is limited to oocyte donation if the patient desires pregnancy (success rate is 40% for this costly intervention that may be undesirable to some women).

The causes of POF into two groups: those in which there is a deficient pool of follicles as in gonadal dysgenesis, or those in which there is accelerated atresia of follicles or disruption of normal ovarian function. Reported causes and/or associations include:

- Causes include the genetic: Turner's syndrome, galactosemia, enzyme deficiencies, abnormal receptor function (abnormal LH and FSH receptors have been reported in several families with familial POF)
- Iatrogenic: pelvic surgery, chemotherapy, XRT, cyclophosphamide
- Viral -- including mumps and CMV in the HIV+ patient
- Idiopathic (the largest subgroup)
- ?Autoimmune oophoritis?

There is evidence that autoimmunity may play a role as a potential cause of POF. Association with other autoimmune diseases has been reported as high as 57%. (Anasti et al.) POF is known to occur as part of one of the polyglandular autoimmune syndrome (types I and II), in which autoimmunity can cause a number of disorders including adrenal insufficiency, hypothyroidism, hypoparathyroidism, vitiligo, myasthenia gravis, and diabetes. The most commonly associated autoimmune disease is hypothyroidism (occurring in 27% of 119 patients prospectively screened by Kim et al.). Another study that looked at forty women with POF found antibodies in 77% of participants. Significantly, they found anti-thyroglobulin antibodies in 29% vs. control 7% (the control population was adult, normal, fertile, and age matched. (Blumenfeld et al.)

There has been a search for organ specific antibodies but no clear associations have yet been found

Proposed antibody targets include: specific anti-ovarian antibodies, steroid-producing cells (especially in patients with both adrenal and ovarian failure), FSH and LH receptors, and the zona pellucida. But overall, no specific antibody has been shown to be reliably associated with premature ovarian failure. An autoimmune etiology for this disorder is also supported by histologic evidence of oophoritis with lymphocytic infiltration in patients who have had ovarian biopsies. However, the incidence of oophoritis and/or pathology of the ovary in POF is unknown -- all studies have been observational/case reports

In addition, due to sampling error, ovarian biopsy is not currently a useful method for diagnosing POF.

Other data that supports and autoimmune etiology for some patients with premature ovarian failure is the occurrence of recovery of ovarian function after immunosuppressive therapy (steroids or otherwise). Again, all studies have been observational or case reports, but there have been documented cases of return of function after treatment of adrenal failure, myasthenia gravis, autoimmune polyglandular failure, and SLE.

Studies thus far have not answered the question of whether steroids can play a role in the treatment of POF. One case report offers a 26 year-old woman in a trial of alternate-day predisone who during treatment resumed spontaneous menstrual bleeding and ovulatory progesterone levels on four occasions. The same article presented a 36 year old woman who got a larger steroid dose (she had been empirically prescribed Dexamethasone 2mg QD for 9 months by her private physician) who unfortunately developed osteonecrosis of the knee.

One study of 11 patients used high-dose, short-term glucocorticoids (Prednisone 25 mg PO QID) x 2 weeks. At this dose side effects were limited to facial rounding, easy bruising, and "mental agitation."

They measured follicular growth, gonadotropin and estrogen levels, as well as ovulation by measuring serum progesterone and/or positive pregnancy test. Of note, 5/11 had other autoimmune diseases (Hashimoto's thyroiditis and RA). Two women spontaneously ovulated; the first patient had three regular ovulatory cycles (after a single course of prednisone) and the other spontaneously ovulated after the first cycle. Both conceived, delivered, and returned to a state of POF after delivery. Both had Hashimoto's thyroiditis, and had been amenorrheic for only 1-2 years.

The only randomized, double-blind, placebo controlled trial looked at whether steroids would influence ovarian responsiveness to exogenous gonadotropins in patients with POF. They planned to randomize 100 patients with idiopathic POF. Their steroid regimen was Dexamethasone 9mg QD x 1 week, which was then tapered to off over the following week (about 1/2 the therapeutic dose used in the other study). They then looked for evidence of follicular development by ultrasound and progesterone level. The study was stopped after there was no ovulation in either group (total 36 patients). Of note, none of these patients had a history of clinical autoimmune disease but 19 had auto-antibodies. (van Kasteren et al).

It is possible that there is a group of patients who would respond to steroid therapy. This study is designed to target a group of patients who are more likely to have POF of an autoimmune etiology.

Primary question:

In a sample of patients with premature ovarian failure and autoimmune thyroid disease, is there a role for treatment with steroids?

Primary outcome: ovulation or pregnancy

B. Study Design and Statistical Analysis

The study with be a multi-center clinical trial at five reproductive endocrinology centers over five years. It will be a prospective, randomized, double-blind, placebo controlled.

Sample size and estimates:

To detect a 20% effect with 80% power at alpha: .05, given a spontaneous ovulation rate of 2.5% over four months (if 20-25% resume ovulation at some point over a period of 1-5 years), there will need to be 50 people per group. This is comparable to the randomized, placebo controlled study mentioned above by van Kasteren.

Intervention:

After randomization, people in steroid arm will start alternate day Prednisone therapy for 16 weeks, with a mean daily dose of 11mg and a total cumulative dose of 1225 mg. This dose was chosen because it is a similar cumulative dose to that that was used in the earlier, smaller trial that possibly showed an effect, but used alternate day dosing which could reduce some of the side effects seen with chronic steroid use. This dose and duration of treatment were chosen based on the available data in the literature, and is more or less an empiric choice. Since POF is not a life threatening disease, aggressive immunosuppression with glucocorticoids is not indicated. This regimen was developed with the objective of giving a dose that might have a beneficial effect yet be less likely to cause serious side effects. Patients and physicians will be blinded to distributed medication, compliance will be determined by pill counting.

Patients who received steroids will start a slow steroid taper (Prednisone 15mg PO QOD x 1 week, then 10mg PO QOD x 1 wk, then 5mg PO QOD x 1 week. If an effect is seen after data analysis, steroid treatment will be offered to subjects who were randomized to placebo.

Ascertainment of response variables:

Blood will be drawn weekly for four months to analyze progesterone levels. Ovulation will be defined as achievement of at least one progesterone level above 3ng/ml (Anasti et al.). Analysis will be done by the chi-squared test, comparing the proportion of women who ovulated in the treatment arm to the same proportion in the non-treatment arm.

C. Study Procedure

Patients will be enrolled using the inclusion/exclusion criteria below. The study will last for four months for each patient. DEXA will be performed on recruitment, and will be offered to the patient at the end of the study as well. Patients will be monitored at monthly intervals by phone interview and physical exam. Blood will be drawn to monitor for hyperglycemia and hypokalemia along with progesterone levels.

D. Study Drugs

Prednisone is an approved drug, which will be taken in the alternate day regimen described above. This is a regimen frequently used for other inflammatory diseases, but since premature ovarian failure is not a life-threatening disease, the risks and benefits will be explained to the patient and the patient will be monitored for the development of side effects. For a description of possible side effects of steroid use, see below.

E. Medical Devices

There are no medical devices being used in this study.

F. Study Questionnaires

Questionnaires will be developed to collect information regarding age and duration of amennorhea to be distributed at the beginning of the study. An additional questionnaire will be developed to assess the possible development of side effects due to prednisone use and will be used monthly for monitoring.

G. Study Subjects

Inclusion criteria:

- Age <40
- Secondary amen > 6 months
- Presence of anti-thyroglobulin and/or anti-thyroid peroxidase (anti-microsomal) antibody -- documented or confirmed by titers. Antithyroglobulin antibody will be detected by the tanned red cell agglutination test, and antimicrosomal antibody will be detected with ELISA.
- Documented FSH >40 IU/L on two separate occasions during previous two months (assay performed as in Anasti et al.)
- Desire for pregnancy -- justifies trial of steroids, a potentially toxic drug
- Three month wash-out period if using HRT
- Exclusion criteria:

- Those with a known possible known cause of POF (Turner's syndrome, galactosemia, history of chemotherapy, RT, pelvic surgery or other cytotoxic drugs such as cyclophosphamide)
- Those with a contraindication to steroids -- these include a history or heart disease, psychoses, osteoporosis, glaucoma or chronic infection including herpes simplex infection. Patients with diabetes or hypertension could enroll with close follow-up.

H. Recruitment of Subjects

Subjects will be referred from a private physician at one of five reproductive endocrinology centers.

I. Confidentiality

A unique code will be assigned to each patient, and will be available only to the investigators.

J. Potential Conflict of Interest

There is no known conflict of interest.

K. Location of the study

One of five reproductive endocrinology centers. At each institution, IRB approval will be required.

L. Potential Risks

On enrollment, informed consent describing the study as well as the risks and benefits will be obtained. It will be described that the may receive either a treatment which may not be effective, or placebo instead of active treatment. If an effect is seen after data analysis, steroid treatment will be offered to subjects who were randomized to placebo. In both cases, patients who came off HRT to participate in the study may see worsening of symptoms related to their low estrogen state. In addition, the risks and benefits of steroid use will be obtained. It will be explained that while the dose and duration of steroid treatment was chosen to minimize known side effects, there is still a risk of even the most serious side effects of steroid treatment, as complications are often not dose- or duration-dependent. These include avascular necrosis, osteoporosis, fracture, and infection , all of which may be delayed effects. A list of possible side effects will be distributed. Patients will be instructed not to stop taking medication without consulting a study physician. They will also be warned that glucocorticoid therapy can stimulate the appetite and cause weight gain, as well as facial rounding, and striae. The symptoms and signs of diabetes and steroid myopathy will be described to the patient. If the patient has diabetes or hypertension, it will be explained that they may see exacerbations of these disease states. Patients may also encounter insomnia, emotional lability. Skin changes including dermal thinning, easy bruising, striae, facial rounding and acne may be encountered.

M. Potential Benefits

The study aims to see an 20%increase in the rate of ovulation in patients who are treated with steroids.

N. Alternative Therapies

Currently, oocyte donation is the only alternative therapy.

O. Compensation to Subjects

There will be no compensation for participation in the study.

P. Costs to Subjects

There will be no costs.

Q. Minors as Research Subjects

There are no minors involved in this study.

R. Radiation or Radioactive Substances

There are no radioactive substances.

F. References

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