Normalization of serum luteinizing hormone levels in women with 46,XX spontaneous primary ovarian insufficiency

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Objective: To determine the proportion of women with primary ovarian insufficiency who achieve normal serum LH levels on transdermal E_2 therapy.
Design: Prospective.
Setting: Clinical research center at a national US health research facility.
Patient(s): Women with spontaneous primary ovarian insufficiency (n = 137) and 70 regularly menstruating control women (n = 70).
Intervention(s): Blood sampled from controls in the midfollicular phase and from patients while they were off E_2 for 2 weeks, then again 3 months later during the E_2-only phase of hormone therapy (E_2 patch [100 μg/d] and oral medroxyprogesterone acetate [10 mg for 12 d/mo]).
Main Outcome Measure(s): Serum LH.
Result(s): While on transdermal E_2 therapy, significantly more women (51.1%, 70/137; 95% confidence interval, 42%, 60%) had serum LH levels in the normal range (5/137, 3.9% at baseline). Mean (SD) serum E_2 level significantly increased on therapy to 95.4 (84.9) pg/mL.
Conclusion(s): A regimen of 100 μg/d of transdermal E_2 therapy achieves normal serum LH levels in approximately one half of women with spontaneous primary ovarian insufficiency. Theoretically, by avoiding inappropriate luteinization, physiologic E_2 therapy may improve follicle function in these women. Controlled studies to assess the effect of transdermal E_2 therapy on follicle function in these women are warranted. (Fertil Steril® 2008;89:429–33. ©2008 by American Society for Reproductive Medicine.)

Key Words: Transdermal estradiol therapy, premature ovarian failure, premature menopause, primary ovarian insufficiency, primary hypogonadism, hypergonadotropic hypogonadism, LH, FSH, hormone therapy

It has been well established that many young women with spontaneous premature ovarian failure have remaining ovarian follicles that may function intermittently, even years after the diagnosis (1–3). There are many reports in the literature of pregnancy developing after the diagnosis has been clearly established. Many of these pregnancies occurred during or soon after estrogen (E) therapy, suggesting that this may be a method for improving fertility in these women (4–6).

Premature ovarian failure, previously known as *premature menopause,* has been defined as the development of hypergonadotropic hypogonadism before the age of 40 years, which is 2 SDs below the mean age of natural menopause (7–9). This condition is associated with amenorrhea, symptoms of E deficiency, and high gonadotropin levels. The incidence is approximately 1 in 250 by age 35 years and is 1 in 100 by age 40 years (10). In reality, the term *premature ovarian failure* is problematic because it implies the permanent cessation of ovarian function. In fact, many women with this condition experience intermittent ovarian function that may last for decades after the diagnosis. Pregnancy may occur in some women many years after the diagnosis (11). Our preferred term for the condition is *primary ovarian insufficiency* (POI), as first introduced by Albright et al. in 1942 (12).

Normally, ovarian follicles grow in response to FSH stimulation, then the midcycle LH surge induces follicle rupture, ovulation, terminal differentiation of granulosa cells into luteal cells, and formation of the corpus luteum (13). In POI, the normal process of ovulation usually fails to occur, despite the presence of antral follicles in $\leq$78% of women with this disorder (2, 3). Many of these follicles fail to function normally because they become luteinized prematurely as a result of the associated chronically elevated serum LH levels (2, 3). This process is akin to

Received October 11, 2006; revised and accepted February 21, 2007.
V.H.V. and L.M.N. are commissioned officers in the United States Public Health Service.
Supported by the Intramural Research Program, National Institute of Child Health and Human Development, National Institutes of Health (Bethesda, Maryland).
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what has been termed the *luteinized unruptured follicle syndrome* (14–16).

Theoretically, E therapy may improve ovulation rates in women with spontaneous POI by reducing the associated chronically elevated serum LH levels to normal. One randomized controlled trial of oral E_2 therapy (2 mg/d) that assessed this found no significant improvement (3). However, the specific agent and route of E administration may differentially affect gonadotropin levels and ovulation rates. The purpose of this study was to define the percentage of women with spontaneous POI who achieve normal midfollicular serum LH levels on a standard regimen of continuous transdermal E_2 therapy.

MATERIALS AND METHODS

Subjects

Between January 2000 and November 2004, we recruited 137 women with spontaneous POI and 70 control women of similar age. The study was approved by the Institutional Review Board of the National Institute of Child Health and Human Development, National Institutes of Health. All women provided written informed consent.

Women With POI

Study patients had to meet the following inclusion criteria: [1] diagnosis of spontaneous POI before the age of 40 years (i.e., $\geq$4 mo of oligo-amenorrhea and two FSH levels in the menopausal range, confirmed on two separate occasions, $\geq$1 mo apart), [2] age between 18 and 42 years, [3] no iatrogenic cause or known chromosomal abnormality, and [4] no contraindication for hormone therapy. Screening baseline evaluation was described elsewhere (17). Because of an administrative error, baseline values for hormone measurements on 11 patients were missing.

Control Women

Control women were healthy, not pregnant, menstruating regularly (cycles between 21 and 35 d), and using no chronic medication or hormonal contraception. They were between the ages of 18 and 42 years.

Protocol

Women with POI were seen for two visits: [1] a baseline screening evaluation at which time they had been off any E–progestin hormone therapy for $\geq$2 weeks and [2] an evaluation after they had been receiving a standardized hormone regimen for $\geq$3 months, consisting of a 100-μg E_2 patch (Vivelle Dot; Novartis, East Hanover, NJ) and cyclic oral medroxyprogesterone acetate (10 mg for 12 d/mo, Provera; Pharmacia and Upjohn, Kalamazoo, MI).

For women with spontaneous POI, blood samples were drawn at baseline (off any E–progestin therapy for $\geq$2 wk) and after $\geq$3 months on the E_2–progestin hormone therapy (during the E_2-only phase of the hormone cycle, not while on progestin). For control women, blood samples were drawn during the midfollicular phase (days 5–12).

Hormone Assays

Follicle-stimulating hormone and LH were measured by microparticle enzyme immunoassay (AxSYM System; Abbott Diagnostics, Abbott Park, IL). For FSH, the intra-assay CV was 4.9%, and the interassay CV was 6.5%; for LH, these were 5.8% and 6.4%, respectively. Estradiol was measured by competitive chemiluminescence immunoassay (Immulite 2000 analyzer; Diagnostic Products Corporation, Los Angeles, CA); the intra-assay and interassay CVs were $<$11.0%. For conversion from conventional units (pg/mL) to SI units, (pmol/L) data may be multiplied by 3.671.

Statistical Analysis

Results are presented as mean $\pm$ SD. All P values are two-tailed and were considered significant at $<$.05. We used SAS, version 6.12 (SAS Institute, Cary, NC) for all analyses. Paired comparisons of clinical characteristics as well as hormone levels were made by using the signed rank test. Comparison of hormone levels between POI and control groups was made by using rank sum test. Multiple regression was used to evaluate the relative influence of several factors on outcome measures. Correlations were assessed by using the Spearman rank correlation.

RESULTS

The normal midfollicular LH and FSH levels in our assays were 3 to 14 IU/L and 3 to 10 IU/L, respectively, on the basis of the 5th and 95th percentiles from 67 control samples. (We excluded 3 control samples that had predefined midcycle LH levels of $>$20 IU/L.)

The POI group (n = 137) did not differ significantly from the control group (n = 67) with regard to mean $\pm$ SD age (30.5 $\pm$ 5.6 y vs. 28.2 $\pm$ 7.2 y), body mass index (23 $\pm$ 3.2 kg/m^2 vs. 22.3 $\pm$ 2.8 kg/m^2), or age of menarche (12.6 $\pm$ 1.5 y vs. 12.4 $\pm$ 1.3 y). In the POI group, the mean age of onset of menstrual abnormalities was 24.6 $\pm$ 8.1 years, age of diagnosis was 28.2 $\pm$ 6.9 years, and mean time since diagnosis at presentation to our study was 40.4 $\pm$ 45.5 months.

In women with POI, the mean (SD) serum E_2 level on therapy increased to 95.4 (84.9) pg/mL [350.21 (311.66) pmol/mL] from 40.0 (42.7) pg/mL [146.84 (156.75) pmol/mL] at baseline ($P<$.001, Fig. 1A). Estradiol therapy significantly reduced serum LH levels, from 52.2 (26.2) IU/L while off therapy to 15.2 (15.7) IU/L while on therapy ($P<$.001). Similarly, FSH levels were reduced from 88.5 (39.3) IU/L to 23.9 (23.7) IU/L ($P<$.001) while on transdermal E_2 therapy.

The proportion of women who had FSH and LH levels in the normal range while receiving transdermal E_2 therapy are shown in Table 1 and Figure 1B. While on transdermal