0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(5):3069–3076

doi: 10.1210/jc.2004-1985

CLINICAL CASE SEMINAR

Selective Theca Cell Dysfunction in Autoimmune Oophoritis Results in Multifollicular Development, Decreased Estradiol, and Elevated Inhibin B Levels

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We describe the clinical course of three women with presumptive autoimmune oophoritis who developed multiple follicles but very low to undetectable estradiol levels. Multiple follicles developed spontaneously in all subjects and during pulsatile GnRH treatment for ovulation induction in subject 1. The development of multiple dominant follicles was accompanied by LH levels in the postmenopausal range and FSH levels at the upper limit for premenopausal women. Serum inhibin B levels were elevated appropriately in the setting of multifollicular development, but estradiol levels remained low. Measurement of estradiol precursors demonstrated androstenedione and estrone levels below the 95th percentile in normal women. Adrenal cortical antibodies, and antibodies to 21-hydroxylase and P450 side chain cleavage enzymes were identified in all subjects. All subjects met the criteria for premature ovarian failure during follow-up. Subject 1 later developed adrenal failure, whereas subject 3 had adrenal failure at the time of the study.

These subjects elucidate the hormonal pattern in autoimmune oophoritis, before the full criteria for premature ovarian failure are met. The elevated inhibin A and B levels, which accompany the development of multiple small and dominant follicles in these women, suppress FSH relative to LH levels, virtually independent of estradiol. These data provide further evidence for an important role of inhibin B and inhibin A in the negative feedback control of FSH. In addition, the normal inhibin A and inhibin B production in the absence of estradiol precursors and estradiol provide insight into the selective dysfunction of the theca cells in autoimmune oophoritis. (*J Clin Endocrinol Metab* 90: 3069–3076, 2005)

PREMATURE OVARIAN FAILURE (POF), defined clinically by amenorrhea in women under 40 yr of age in association with elevated serum gonadotropin concentrations, implies the end stage of ovarian dysfunction. However, longitudinal studies have shown that ovarian activity waxes and wanes in this disorder and that follicle development is common, occurring in up to 84% of women with POF (1–3). FSH levels may be suppressed to the normal range in the presence of follicular development and ovulation; however, they remain at the upper limit of normal and are higher, on average, than in regularly cycling women (1). It has been demonstrated that an elevated FSH level, greater than 1 SD above the mean for healthy women, in association with regular or slightly irregular menstrual cycles predicts a poor response to assisted reproductive technology and that the elevated FSH identifies decreased "ovarian reserve," a term that encompasses follicle number and function (4). Therefore, it has been postulated that women less than 40 yr of age with predominantly regular cycles and elevated FSH levels are in the early stages of POF or have a mild form of POF, termed "incipient" or "occult" POF (5–8). Although formal longitudinal studies have not been performed to document a continuum between incipient or occult POF and POF, a small study demonstrated that 11 of 13 of these women subsequently developed amenorrhea and POF (6).

Patients with POF exhibit low serum concentrations of estradiol, inhibin A, and inhibin B due to a decreased number of follicles and the absence of follicle development (3, 6, 9). During the intermittent follicle development that occurs in POF, serum inhibin A and inhibin B concentrations are also low, but estradiol can be elevated compared with regularly cycling women (3). A similar pattern of low inhibins and increased estradiol has been demonstrated in women with occult ovarian failure, *i.e.* regular menstrual cycles and elevated FSH levels (6). In contrast to this typical pattern, we and others have identified a subset of women with amenorrhea in whom multiple large follicles develop in conjunction with low levels of estradiol (3, 10–13). On presentation, these women had normal to mildly elevated FSH levels, which did not reach the postmenopausal range. We have recently shown that inhibin B is elevated in one such patient (3). Longitudinal examination of three women with this hormonal pattern provides evidence that these hormonal changes are due to presumptive autoimmune oophoritis. Autoimmune oophoritis is also a precursor to POF and these

First Published Online February 10, 2005

Abbreviations: ACA, Adrenocortical antibodies, CV, coefficient of variation; 17OH, 17-hydroxy; 17αOHAb, 17αhydroxylase antibody; 21OHAb, 21-hydroxylase antibody; p450scc, p450 side chain cleavage; P450sccAb, P450scc antibody; POF, premature ovarian failure; StCA, steroid cell antibody.

women subsequently developed the full criteria for the diagnosis of POF.

Case Reports

Subject 1 was a 31-yr-old female who presented with 2 yr of amenorrhea. The subject had a history of regular menstrual cycles complicated by painful ovarian cysts. She was treated with birth control pills for 2 yr, and developed amenorrhea after she stopped treatment. Her past medical history was remarkable for hypothyroidism diagnosed at age 11 yr and treated with thyroid hormone replacement. She did not smoke cigarettes. Her physical exam was unremarkable.

Subject 2 was a 35-yr-old female who presented with a 1 yr history of amenorrhea, hot flashes, vaginal dryness and poor sleep. The subject had a normal pregnancy and delivery three years earlier. Her past medical history was remarkable for primary hypothyroidism, treated with thyroid hormone replacement. She stopped smoking 5 yr before her presentation. Family history was remarkable for multiple sclerosis. Her physical exam was unremarkable.

Subject 3 was an 18-yr-old female with a history of irregular menstrual cycles and menometrorrhagia since menarche at age 13 yr. She was treated with a birth control pill for 1 yr, and presented with a 9-month history of amenorrhea after stopping treatment. Review of systems was notable for fatigue, salt craving, and hot flashes. Her family history was remarkable for multiple sclerosis, premature graying, and hypothyroidism. Her physical exam demonstrated the absence of orthostatic signs.

None of the subjects had a history of eating disorders, excessive exercise, low weight, hirsutism, acne, galactorrhea, visual changes, or headaches. The clinical features and initial laboratory results of the three subjects are outlined in Table 1.

Subjects and Methods

All studies described herein were approved by the Partners Human Research Committee and all subjects gave written informed consent.

TABLE 1. Clinical and hormonal characteristics of three subjects with amenorrhea at the time of presentation

	Subject no.		
	1	2	3
Age (yr)	31	35	18
Duration of amenorrhea (yr)	2	1	0.75
FSH (IU/liter) (postmenopausal ≥40)	19.9	26.2	20.4
LH (IU/liter) (postmenopausal ≥40)	42	49.1	92.5
Estradiol (pg/ml) (early follicular phase 20–113)	<20	ND	74
Ultrasound (no. of follicles)			
11–15 mm	4	0	8
16–30 mm	4	3	2
Ovarian antibodies	ND	Negative	Positive
Hypothyroidism	Yes	Yes	No
TSH (μU/ml) (0.5–5)	2.27[a]	4.74[a]	1.30
Thyroid autoantibodies	Negative	Negative	Positive
Cortisol 1 h after ACTH (>18 μg/dl)	39.5	ND	9.1
ACTH (6–76 pg/ml)	ND	ND	449
Adrenocortical antibodies[b]	Negative	Negative	Positive
Addison's disease	No	No	Yes

ND, Not done.

[a] On treatment with thyroxine.

[b] Adrenal cortex antibodies obtained from clinical laboratories at the time of presentation.

For purposes of this study, POF was defined as 6 months of amenorrhea with two FSH levels greater than or equal to 40 IU/liter Second International Reference Preparation human menopausal gonadotropin, which represents the upper 95% confidence limit of the midcycle FSH peak in 118 normal menstrual cycles (1) in women under the age of 40 yr. In subject 1, the serum FSH concentration was greater than 1 SD above the mean for regularly cycling women (18.5 IU/liter); however, it did not reach postmenopausal levels (≥40 IU/liter). Therefore, her diagnosis was unclear and she underwent ovulation induction with three cycles of pulsatile GnRH stimulation for anovulatory infertility (14, 15). GnRH 75 ng/kg/bolus was administered at a variable frequency designed to reproduce that in the normal menstrual cycle (15). Blood samples were drawn daily for measurement of LH, FSH, estradiol, progesterone, inhibin A, and inhibin B. Ultrasounds were performed on approximately d 6, then every 3–4 d until there was evidence of a corpus luteum as indicated by follicle collapse (1) or the appearance of internal echoes in the largest follicle on ultrasound.

Subject 2 underwent blood sampling and ultrasounds weekly for 12 wk, with the first 6 wk on no estradiol treatment and the second 6 wk on estradiol 2 mg per day, as part of a larger study (1). Subject 3 had blood sampling and an ultrasound on a single day.

Ultrasounds were performed using a Sonolayer L, SAL-778 machine (Toshiba Corp., Tokyo, Japan). All follicles at least 10 mm in maximal diameter were documented.

Assays

LH, FSH, estradiol, and progesterone were analyzed by RIA (subjects 1 and 2) (16, 17) or using a two-site monoclonal nonisotopic system (subject 3; LH, FSH and estradiol; AxSYM, Abbott Laboratories, Abbott Park, IL) and a sequential competitive immunoassay (subject 3; progesterone; Immulite, Diagnostic Products Corp., Los Angeles, CA) (18, 19). The gonadotropin assays were calibrated using the same reference preparation, and gonadotropin levels were not significantly different using the two assays across a broad range of values, as previously described (18). Gonadotropin levels are expressed in international units per liter, as equivalents of the Second International Reference Preparation 71/223 of human menopausal gonadotropins. For the AxSYM LH, the interassay coefficients of variation (CVs) were 5.3, 5.5, and 7.4% for quality control sera containing 5.6, 26.2, and 69.0 IU/liter, respectively. For the LH RIA, the interassay CVs were 6.0 and 11.4% for quality control sera containing 10.3 and 24.6 IU/liter, respectively. For the AxSYM FSH, the interassay CVs were 6.9, 7.1, and 6.3% for quality control sera containing 4.3, 35.4, and 79.5 IU/liter, respectively. For the FSH RIA, the interassay CVs were 8.4 and 11.8% for quality control sera containing 7.7 and 21.9 IU/liter, respectively. To conserve serum, the estradiol assay was performed with lower preextraction serum volumes, yielding a sensitivity of 40 pg/ml for blood samples in subjects 1 and 2 (1). For the AxSYM estradiol assay, the interassay CVs were 10.2, 6.5, and 8.2% for quality control sera containing 81, 284, and 683 pg/ml (297, 1042, and 2507 pmol/liter), respectively. For the estradiol RIA, the interassay CVs were 6–13% for quality control sera at low, medium, and high levels within the range of the assay. For the Immulite progesterone assay, the interassay CVs were 14.4, 10.6, and 10.8% for quality control sera containing 1.5, 3.2, and 14.3 ng/ml (4.8, 10.2, and 45.5 nmol/liter), respectively. For the progesterone RIA, the interassay CVs were 9–12% for quality control sera at low, medium, and high levels within the range of the assay.

Inhibin A and B were measured by ELISA (Serotec, Oxford, UK). The inhibin A assay uses a lyophilized human follicular fluid calibrator standardized as equivalents of the World Health Organization recombinant human inhibin A preparation 91/624, and values are reported as international units per milliliter. The interassay CVs for the dimeric inhibin A assay were 11.7 and 10.3% for quality control sera containing 5.01 and 10.01 IU/ml, respectively. For inhibin B, the intraassay CVs were 4–6% and the interassay CVs were 15–18% for quality control sera containing 121, 250, and 723 pg/ml, respectively. Total testosterone, androstenedione, and 17-hydroxy (17OH) progesterone were measured using a RIA (Coat-a-Count; Diagnostic Products Corp., Los Angeles, CA). For total testosterone, the interassay CVs were 7.3, 8.1, and 6.0% for quality control sera containing 188, 454, and 948 ng/dl (8.4, 20.3, and 42.3 nmol/liter). For androstenedione, the interassay CVs were 8.7 and 6.2% for quality control sera containing 1.04 and 4.80 ng/ml (3.63 and 16.8 nmol/liter). For 17OH progesterone, the interassay CVs were 11.9, 6.6,

and 7.2% for quality control sera containing 0.45, 1.73, and 5.3 ng/ml (1.36, 5.23, and 16.0 nmol/liter). Estrone was measured using a RIA (Diagnostic Systems Laboratories, Inc., Webster, TX). For estrone, the interassay CVs were 9.2 and 4.1% for quality control sera containing 35 and 300 pg/ml (129.5 and 1110 pmol/liter).

All samples were analyzed in duplicate except for inhibin B, which was analyzed once, and all samples from an individual were analyzed in the same assay.

Adrenocortical antibodies (ACA) were evaluated by indirect immunofluorescence against bovine adrenal gland using serial 2-fold dilutions of subject serum (20). Steroid cell antibodies (StCA) were detected by indirect immunofluorescence against monkey ovary and testis (Bios GmbH, Grafelfing, Germany). Indirect immunofluorescence assays are expressed as the lowest 2-fold serial dilution of subject serum with a positive result. 21-hydroxylase antibody (21OHAb), 17α-hydroxylase antibody and P450 side chain cleavage antibody (P450sccAb) were measured using radiobinding assays to recombinant human 21OH, 17α-hydroxylase and P450 side chain cleavage (P450scc) radiolabeled with ^{35}S as previously described (21, 22). Antibody levels were expressed as relative indices (mean cpm unknown − mean cpm 2 negative standards)/(mean cpm positive standard − mean cpm 2 negative standards), with the upper limit of normal defined as the mean + 3 SD of 90 healthy controls.

Results

Subject 1 underwent three cycles of pulsatile GnRH treatment, with cycle 2 commencing 2 months after menses resulting from cycle 1, and cycle 3 commencing 1 month after spotting from cycle 2. All cycles of GnRH treatment resulted in the development of multiple dominant follicles; six in cycle 1, eight in cycle 2, and seven in cycle 3 (Fig. 1). During all three pulsatile GnRH treatment cycles in subject 1, the FSH levels increased above the normal range in the early follicular phase and remained elevated throughout the cycle (Fig. 1), in contrast to the normal levels typically observed in GnRH-deficient women on pulsatile GnRH treatment (23). However, FSH reached the postmenopausal range for this assay (>40 IU/liter; Ref. 1) on only 1 d during cycle 2. LH was elevated above the postmenopausal range throughout the three cycles. Despite the development of six to eight dominant follicles, estradiol levels reached a maximum of only 112 pg/ml (411 pmol/liter) in cycle 1 and 135 pg/ml (495 pmol/liter) in cycle 2, and did not increase at all in cycle 3. In contrast, inhibin B levels were 3- to 6-fold greater than the upper limit for normal women in the follicular phase (mean + 2 SD; 173 pg/ml) in cycles 1–3, and reached levels similar to those measured at the time of hCG administration during controlled ovarian stimulation for *in vitro* fertilization (mean ± SE; 1242 ± 100 pg/ml; Ref. 24).

To determine whether low serum estradiol concentrations were related to decreased precursor production, androstenedione and estrone levels were measured. In all cycles, androstenedione and estrone levels were equal to or less than 1 SD below the mean for normal subjects (Fig. 2). Serum testosterone was similarly decreased below normal.

Although inhibin A and progesterone reached the normal range for women with regular menstrual cycles and one corpus luteum (25), two corpora lutea were present in cycles 1 and 3 as assessed by the development of internal echoes in two of the follicles. Thus, inhibin A and progesterone levels

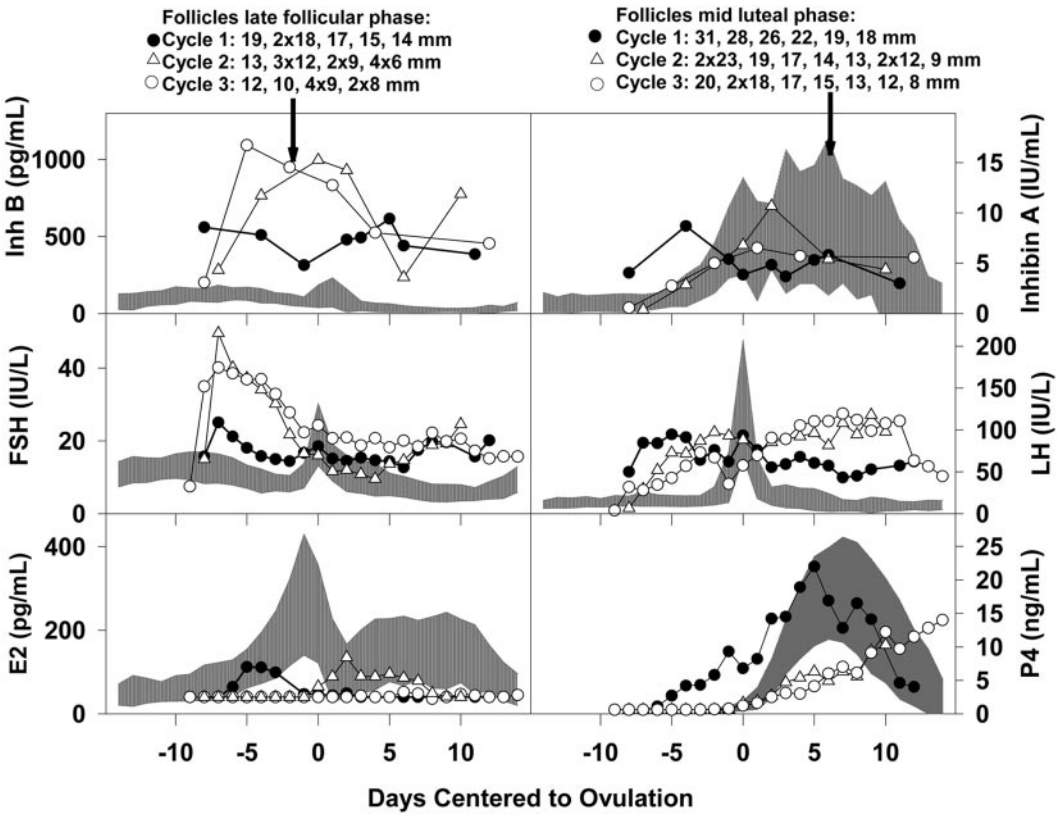

FIG. 1. Inhibin B (Inh B), FSH, estradiol (E2), inhibin A (Inh A), LH, and progesterone (P4) in subject 1 during three cycles of treatment with pulsatile GnRH (cycle 1, ●; cycle 2, △; cycle 3, ○). The *shaded area* depicts the mean ± 1 SD in regularly cycling women (25). The data were centered to the day the progesterone reached at least 1 ng/ml in cycles 2 and 3 because there was no clear LH surge.

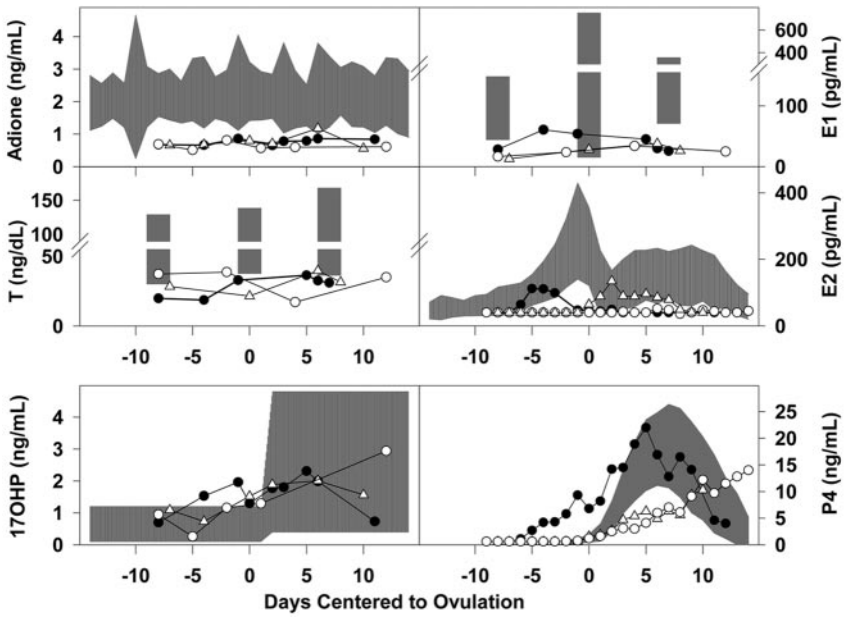

FIG. 2. Androstenedione (Adione), testosterone (T), estrone (E1) and estradiol (E2), and 17OH progesterone (17OHP) and progesterone (P4) in subject 1 during three cycles of treatment with pulsatile GnRH (cycle 1, ●; cycle 2, △; cycle 3, ○). The *shaded area* depicts the mean ± 1 SD in regularly cycling women (25, 65). The data were centered to the day the progesterone reached at least 1 ng/ml in cycles 2 and 3 because there was no clear LH surge.

were at the middle to lower range for levels achieved in the midluteal phase in women with greater than one corpus luteum [progesterone 19.7 ± 3.0 ng/ml (62.6 ± 9.5 nmol/liter) and inhibin A 10.4 ± 1.3 IU/ml] (19). In addition, progesterone continued to increase in the late luteal phase in cycles 2 and 3 instead of exhibiting the normal luteal phase decrease that occurs in the absence of pregnancy.

To determine whether progesterone products were affected, serum 17OH progesterone levels were measured. Similar to progesterone, 17OH progesterone levels reached the normal range in the luteal phase (Fig. 2).

Subject 2 was followed for 6 wk, with 2 wk of additional follow-up 13 months later. The initial ultrasound demonstrated six dominant follicles of 11–38 mm, which decreased in size, leaving three dominant follicles at the end of wk 2. One new dominant follicle appeared at the end of wk 2, two each at the end of wk 4 and 5, and two at the end of wk 6, resulting in eight dominant follicles 10–24 mm at the end of wk 6. Subject 3 had two dominant follicles at the time of her ultrasound. In subjects 2 and 3, serum FSH concentrations were elevated above the normal range during spontaneous follicular development but reached the postmenopausal range (>40 IU/liter; Ref. 1) only in subject 3 (Table 2). Interestingly, LH levels were much higher than FSH levels and reached the postmenopausal range in both subjects (Table 2). Estradiol was below the limit of detection (subject 2) or normal (subject 3), despite the development of more than one dominant follicle. Inhibin B was at the upper limit in normal women in subject 3 and 2- to 5-fold above the upper limit in normal women in subject 2, similar to the inhibin B levels during assisted reproduction (24) and consistent with multiple follicle development. Inhibin A was in the normal range in both subjects. Progesterone was elevated above the follicular phase range at the time of the baseline ultrasound [3.92 ng/ml (12.5 nmol/liter)] and on d 42 of monitoring [3.3 ng/ml (10.5 nmol/liter)] in subject 2, but decreased to follicular phase levels in the intervening weeks, with no spontaneous vaginal bleeding. In subjects 2 and 3, estrone, androstenedione, and testosterone were equal to or greater than 1 SD below the normal limit and 17OH progesterone was within normal limits despite the development of multiple dominant follicles (Table 2).

Based on the presumably acquired estradiol deficiency in these patients, steroid cell (StCA), adrenal cortical (ACA),

TABLE 2. Hormone levels in subjects 2 and 3

	Dominant follicles (mm)	LH (IU/liter)	FSH (IU/liter)	E2 (pg/ml)	P4 (ng/ml)	Inh A (IU/ml)	Inh B (pg/ml)	ADione (ng/ml)	T (ng/dl)	E1 (pg/ml)	17OHP (ng/ml)
Subject 2											
day of monitoring											
30	21, 2 × 10	61.4	30.5	<40	1.4	5.4	324	0.6	16	ND	0.4
36	25, 21, 2 × 13, 11	84.2	29.1	<40	1.7	6.1	848	0.3	29	20	0.5
42	24, 21, 20, 13, 2 × 12, 2 × 10	46.4	23.2	<40	3.3	6.9	367	0.3	11	ND	ND
457	16, 14, 2 × 13, 2 × 10	100	38.8	<40	2.0	8.1	493	0.4	15	ND	0.6
Subject 3	17, 11	156	55.4	56	0.5	6.5	183	1.4	5	ND	0.5
day 31 after last menses											

E2, Estradiol; P4, progesterone; Inh A, inhibin A; Inh B, inhibin B; ADione, androstenedione; T, total testosterone; E1, estrone; 17OHP, 17 hydroxy progesterone; ND, not done. Premenopausal follicular phase ranges: LH, 3.2–44.7 IU/liter; FSH, 3.9–39 IU/liter; E2, 20–271 pg/ml; P4, 0.1–1.2 ng/ml; Inh A, 0.6–5.1 IU/ml; Inh B, 36–173 pg/ml; ADione, 0.5–3.85 ng/ml; T, 5–63 ng/dl; E1, 44.5–148.1 pg/ml. Premenopausal luteal phase ranges: P4, 6.0–24 ng/ml; 17OHP, 0.4–4.8 ng/ml; Inh A, 0.6–13.8 IU/ml. To convert to SI units, multiply E2 by 3.671, P4 by 3.18, AD by 3.492, T by 4.467, E1 by 3.7, and 17OHP by 3.026.

P450sccAb, 21OHAb, and 17αhydroxylase antibody (17αOHAb) were measured (Table 3). All subjects had a positive titer for adrenal cortical antibodies, 21OHAb and P450 side chain cleavage antibodies. Subjects 1 and 3 had positive titer for StCA and only subject 1 had a positive titer for 17α-hydroxylase antibodies.

Follow-up history was available for subjects 1 and 3. Two years after her presentation, subject 1 developed achy joints and a positive ANA titer. Three years later, her ovaries became inactive and her FSH rose into the postmenopausal range. Nine years later she developed primary adrenal failure. Subject 2 continued to have multifollicular development and amenorrhea and her FSH rose to the postmenopausal range 1.5 yr after her presentation (maximum FSH, 63.1 IU/liter). She was subsequently lost to follow-up. Subject 3 continued to have irregular menstrual cycles and intermittent amenorrhea for up to 6 months over the next 9 yr. Her FSH level rose to the postmenopausal range 17 months after her initial presentation, during an episode of amenorrhea. She also developed subclinical hypothyroidism 8 yr later.

Discussion

The women described herein have presumptive autoimmune oophoritis (26). Although a histological diagnosis is not available, adrenal failure at the time of presentation (one of three) and/or positive adrenal cortical (ACA) and 21OHAb (three of three), which indicate the potential to develop clinical or subclinical adrenal insufficiency (27), are highly suggestive of this process (28, 29). In fact, subject 1 later developed adrenal failure in addition to hypothyroidism and POF and subject 3 developed hypothyroidism in addition to adrenal failure and POF, meeting the criteria for autoimmune polyglandular syndrome type II (30). Subject 2 also manifested hypothyroidism and POF suggesting autoimmune polyglandular syndrome type II, but has been lost to follow-up.

In patients with autoimmune adrenal failure, antibodies to the adrenal cortex (ACA) and to steroid cells (StCA) have been identified by indirect immunofluorescence on fixed tissue samples (reviewed in Ref. 31). StCA are a subset of ACA because they react not only with the adrenal cortex, but also with the cytoplasm of steroid producing cells in the ovary, testis, and placenta. StCA are present in 60–87% of women with secondary amenorrhea and adrenal autoimmunity and/or Addison's disease (26, 29, 32), similar to the prevalence in the current subjects (two of three), but in only up to 10% of women with idiopathic POF not associated with adrenal disease (26, 31, 33–35). Therefore, it has been suggested that StCA best discriminate autoimmune POF from POF of other etiologies (31, 35).

Recent work has identified the targets of ACA and StCA. The adrenal p450c21 hydroxylase enzyme is the major autoantigen for ACA (36, 37) and the P450scc and 17α-hydroxylase enzymes are the major autoantigen targets of StCA (27, 33, 38). Antibodies to 21-hydroxylase were found in 100% of women with POF and adrenal autoimmunity who are ACA positive (34). Antibodies to P450scc and 17α-hydroxylase enzymes were found in a majority of women with POF and adrenal autoimmunity who are StCA positive, with antibodies to P450scc enzyme found more commonly than antibodies to the 17α-hydroxylase enzyme (35, 39). The results of the current study are consistent with previous findings as 21OH and P450sccAb were found in all three subjects, whereas 17αOHAb were demonstrated in only one subject.

Our longitudinal examination of both spontaneous and GnRH stimulated follicle development in women with presumptive autoimmune oophoritis provides new insights into the follicular and hormonal changes that occur in this disorder. Most remarkable is the spontaneous growth of multiple dominant follicles in the absence of detectable estradiol production (subject 2) and the abnormally low estradiol production in relation to the number of dominant follicles stimulated by exogenous GnRH (subject 1). Previous case reports have demonstrated ovaries with multiple cysts in patients with autoimmune oophoritis (11–13, 40–45), however, estradiol measurements were not always documented coincident with ovarian imaging or surgery, making it unclear whether these were normal follicles or nonfunctioning cysts.

TABLE 3. Antibody levels in women with autoimmune oophoritis, low estradiol, and elevated inhibin B

	Subject no.			Control[c]
	1[a]	2[b]	3	
Androstenedione (ng/ml)	0.6–0.8	0.3–0.6	1.4	ND[d]
Estrone (pg/ml)	28.3–60.6	20.2	ND	ND
Estradiol (pg/ml)	44–111	<40	56	ND
Inhibin B (pg/ml)	509–996	493–848	183	ND
Inhibin A (IU/ml)	6.5–8.7	5.4–8.1	6.5	ND
ACA	**1:64**	**1:32**	**1:64**	Negative
21OHAb (<0.1 = Neg)	**0.981–1.117**	**0.759–0.944**	**0.804**	0
StCA	**1:56–1:112**	Negative	**1:28**	Negative
P450sccAb (<0.1 = Neg)	**0.768–0.796**	0.03–**0.278**	**0.845**	0.004
17αOHAb (<0.1 = Neg)	**0.192–0.741**	0–0.011	0.089	0

Bold values are abnormal. ND, Not done.

[a] Subject 1 had antibodies measured on three occasions separated by 3 and 1 months. A range of hormone levels and antibody titers are given for the individual measurements.

[b] Subject 2 had antibodies measured on four occasions, each separated by 1 month. A range of hormone levels and antibody titers are given for the individual measurements.

[c] Control subjects had normal menstrual cycles and no reproductive dysfunction.

[d] Premenopausal follicular phase ranges: androstenedione, 0.5–3.85 ng/ml; estrone, 44.5–148.1 pg/ml; estradiol, 20–271 pg/ml; inhibin A, 0.6–5.1 IU/ml; inhibin B, 36–173 pg/ml. To convert to SI units multiply androstenedione by 3.492, estrone by 3.7, and estradiol by 3.671.

The inhibin data from the subjects in the current case report demonstrate that these ovarian cysts are functioning follicles and that they fail to produce normal levels of estradiol due to a decrease in the androstenedione and estrone precursors. As a result of the low estradiol levels, the endometrial lining is thin and amenorrhea develops. The absence of normal estradiol negative feedback results in relatively increased FSH levels, which drive further follicle formation.

In contrast to the decreased theca cell androstenedione and consequently estradiol production, the current study demonstrates that granulosa cell inhibin A and inhibin B production is spared. The antibodies and the lymphocytic infiltrate in autoimmune oophoritis selectively target ovarian steroid secreting cells such as theca and hilar cells. Primordial and primary follicles, which secrete inhibin B selectively (46), are spared. Similarly, granulosa cells in developing follicles are spared until they are luteinized by LH and produce steroids (11, 13, 31, 41, 45, 47–50). Thus, granulosa cell inhibin A and inhibin B production from developing follicles is maintained before luteinization. Inhibin B levels are in fact elevated, consistent with the increased number of dominant follicles compared with normal cycling women. These high to normal inhibin A and inhibin B levels stand in contrast to the levels in women with POF of nonautoimmune etiology in which levels are very low, likely related to the paucity of remaining ovarian follicles (9).

Progesterone is a product of luteinized granulosa cells, a target of the autoimmune destruction (11, 13, 31, 41, 45, 47–50). However, there is a relatively short time frame for luteinized granulosa cells to be compromised compared with theca cells, because they luteinize and produce steroids only after the LH surge. Thus, 17OH progesterone and progesterone production are spared, although slightly low in the setting of the multiple dominant follicles that developed. Alternatively, it is possible that the persistently low levels of progesterone in this study and others (40) result from the formation of luteinized, unruptured follicles, which are associated with relatively low progesterone levels compared with those in the normal luteal phase (51). In the current study, the formation of luteinized, unruptured follicles is suggested by dominant follicle growth but failure of the follicles to collapse on ultrasound despite a rise in progesterone.

The remarkable decreases in estradiol precursor levels and sparing of inhibin A and B production suggest a specific and pathogenic relationship between antibodies to P450scc or 17α-hydroxylase enzyme in the theca cell and decreased production of androstenedione. However, it remains unclear whether these antibodies are pathogenic or an epiphenomenon. One could speculate that the decreased estradiol levels from cycle 1 to cycle 3 in subject 1 resulted from stimulation of immune activity against theca cells, resulting in increased destruction. Indeed, gonadotropins have been demonstrated to increase HLA-DR expression on granulosa cells (52). Previous data demonstrated that the sera of patients with autoimmune failure type I was cytotoxic to cultured luteinized granulosa cells, although it was also toxic to follicular phase granulosa cells, which do not produce steroids (53). Furthermore, antibodies to the 21-hydroxylase enzyme in the serum of patients with autoimmune Addison's disease inhibit enzyme activity *in vitro* (54); however, no functional enzyme defects could be identified *in vivo* (55). Thus, the potential pathogenic role of autoantibodies requires further investigation.

The data in the current report point to the importance of estradiol, inhibin A, and inhibin B in FSH-negative feedback. There is increasing evidence that inhibin B and inhibin A play a tonic role in FSH negative feedback, *i.e.* in the setting of ovarian aging (25, 56, 57). However, the relative role of inhibin A and inhibin B in dynamic FSH suppression during the menstrual cycle remains controversial (58). FSH was increased above the normal range in all subjects in the current study, attesting to the importance of estradiol in FSH negative feedback. Nevertheless, it was much lower than the 95% confidence limit of 132.1–165.1 IU/ml for 45- to 55-yr-old postmenopausal women using the same assay and lower than levels in women with hypergonadotropic hypogonadism of a nonautoimmune etiology (1, 3, 9, 59). Thus, these data provide further evidence for the tonic control of FSH by the inhibins, although both estradiol and the inhibins are clearly required to maintain FSH levels in the normal range. This work also identifies inhibin as the nonsteroidal factor originally hypothesized by Leer *et al.* (10) to selectively feed back on FSH in women with autoimmune oophoritis, resulting in the normal FSH but postmenopausal LH levels seen in this and other studies (10–13, 49). Finally, it may be important to assess underlying follicular development with an ultrasound examination or inhibin B measurement when evaluating patients presenting with amenorrhea and FSH levels in the upper normal range as these studies could raise suspicion for autoimmune oophoritis if multifollicular development is identified.

At presentation, autoimmune oophoritis appears to fit on a continuum with POF; however, its trajectory may be different than that of incipient or occult ovarian failure. Patients with both incipient/occult ovarian failure (5–8) and autoimmune oophoritis in this case report and others (10), presented with elevated FSH levels compared with those in regularly cycling women but FSH did not reach the postmenopausal range. However, women with incipient/occult ovarian failure had regular or slightly irregular cycles and normal estradiol levels, whereas those with autoimmune oophoritis in the current study and others presented with very low estradiol levels, LH levels in the postmenopausal range and were amenorrheic for 9 months to 3 yr (10–12, 41). Furthermore, the first subject in this case report had excellent follicular growth in response to exogenous GnRH suggesting that fertility is possible in women with autoimmune oophoritis, whereas those with incipient/occult ovarian failure have a poor follicular response to ovulation induction (5, 6). Indeed, there are multiple case reports in which corticosteroid treatment results in the resumption of menstrual cyclicity in women with autoimmune oophoritis after as many as 3 yr of amenorrhea (reviewed in Ref. 60) although randomized, controlled trials are necessary to confirm these findings (61).

Regardless of the trajectory, POF is the clinical endpoint for women with autoimmune oophoritis (13, 50). Nevertheless, it is unclear whether the same end stage ovary occurs in autoimmune oophoritis as in other forms of POF or

whether primordial follicles remain in women with autoimmune oophoritis, as suggested by the sparing of primordial follicles on histology (11, 13, 31, 44, 45, 47–50) and a case report of pregnancy 13 yr after the diagnosis of POF (62). One report suggests that the number of primordial follicles is decreased even if they are spared (48) and small ovaries have been reported in women with POF and autoimmune adrenal disease (44, 49). In our own series, subject 1 did develop inactive ovaries and FSH levels in the postmenopausal range 3 yr after her presentation, fulfilling the full criteria for POF; subject 2 remained amenorrheic despite the continued development of multiple follicles for the 1.5 yr of follow-up with FSH rising into the postmenopausal range in a majority of the later measurements; and subject 3 experienced up to 6 months of amenorrhea at a time over the next 10 yr, during which FSH levels increased into the postmenopausal range. The relative FSH suppression despite amenorrhea during the early stages of autoimmune oophoritis and the possible differences in fertility in women with autoimmune oophoritis despite a potentially similar clinical endpoint as for other forms of POF highlight the overwhelming need for better definitions and terminology for the disorders we collectively term POF.

Between 2 and 10% of POF is associated with adrenal failure or autoimmunity (26, 63). Adrenal failure with subsequent ovarian failure occurs in 40% of females with positive StCA (26), as was true in subject 3. In contrast, ovarian failure can precede adrenal failure by 8–14 yr (43, 47), as occurred in the first subject who developed adrenal failure 9 yr after her presentation with POF. Adrenal failure presenting after ovarian failure emphasizes the importance of taking a careful history for symptoms of adrenal insufficiency at presentation and follow-up. Adrenal antibodies (ACA and/or 21OHAb) should also be assessed in any woman with POF because they are predictive of clinical adrenal failure (27) and increase the pretest probability of detecting an abnormal cortisol response to ACTH stimulation (64). However, the absence of adrenal antibodies does not rule out later adrenal insufficiency, as illustrated by subject 1. It also appears that thyroid autoimmunity is slightly more common in women with POF in the absence of adrenal failure (14%), compared with the normal population (31) and is the most common autoimmune abnormality accompanying POF (26). Two of the subjects presented here had hypothyroidism at the time of presentation and the third subsequently developed it. Thus, a careful eye to both adrenal insufficiency and hypothyroidism are warranted in all women with POF.

The three cases presented again emphasize the development of multiple follicles in autoimmune oophoritis. The longitudinal examination in both spontaneous and stimulated cycles demonstrates the failure of estradiol production resulting from presumed autoimmune destruction of cells producing estradiol precursors. In contrast, granulosa cell sparing results in appropriately elevated inhibin B levels. Consequently, FSH levels are elevated above normal but suppressed below the range in postmenopausal women and other subsets of women with POF. These data provide further evidence for the importance of the inhibins in FSH negative feedback and suggest a careful assessment of ovarian activity is necessary in the evaluation of amenorrhea.

Acknowledgments

We thank Judith Adams, D.M.U., for her expert ultrasonographic assistance and Patrick Sluss, Ph.D., for his expertise in reproductive assays.

Received October 7, 2004. Accepted February 1, 2005.

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This work was supported by National Institutes of Health Grants U54 HD29164 and M01 RR1066.

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