0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 4
Printed in U.S.A.

CLINICAL CASE SEMINAR

The Resistant Ovary Syndrome in a Patient with Galactosemia: A Clue to the Natural History of Ovarian Failure

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A 16-yr-old female (date of birth, November 26, 1974) was seen for ongoing management of galactosemia and hypergonadotropic hypogonadism. She had developed jaundice 10 days postnatally, with vomiting and failure to gain weight. Galactosemia was diagnosed on the basis of elevated blood and urinary galactose and was confirmed by absent red cell galactose-1-phosphate uridyl transferase. The patient was commenced on a strict lactose-free diet, which was liberalized from age 4–9 yr. At the age of 11 yr, a high basal FSH level (Table 1) was demonstrated. At age 13 yr, 3 months, her physical appearance remained prepubertal. Serum gonadotropin levels were elevated, and serum estradiol was 43 pmol/L (Table 1). Ethinyl estradiol treatment (10 μg/day) was commenced. Menarche occurred at age 14 yr (November 1988), and an additional three menstrual periods followed over the next 10 months; the last two were 1 month apart. At age 14 yr, 11 months, she was obese. Breast development was reported as Tanner stage III and pubic hair as Tanner stage I. Bone age was 12.25 yr (according to the criteria of Greulich and Pyle; 1a). Ethinyl estradiol treatment (10 μg/day) was continued.

She was first seen at our institution in February 1991 (aged 16 yr, 3 months). She was following a strict lactose-free diet and taking ethinyl estradiol (10 μg/day) and a calcium supplement. Her weight was 81.6 kg, and her height was 154.5 cm. Blood pressure was 130/70 mm Hg. Visual acuity was 20/20 in both eyes, with no lens opacity. She was sexually mature, but with poorly developed nipples. She had regular monthly vaginal bleeds lasting at least 3 days. Her karyotype was 46,XX.

In April 1991 while receiving estradiol treatment, gonadotropin levels were elevated, and progesterone was in the nonluteal range (Table 1). Serum PRL was normal at 81 IU/mL. Bone age was 15.5 yr. Ethinyl estradiol treatment was stopped, and a 2-month period of amenorrhea followed. Gonadotropin levels off therapy were elevated (Table 1).

Ethinyl estradiol (10 μg/day) was reintroduced in July 1991. Menstrual periods occurred in November and December 1991. In December 1991, Provera (10 mg/day for days 1–12 every second month) was added to the replacement therapy. In May 1992, regular hormone replacement therapy was stopped. Despite this, her menstrual cycle remained regular, with a 24- to 28-day cycle, until March 1993. In February 1993, with no therapy, FSH and LH levels were normal (Table 1). Luteal phase measurements of serum progesterone and estradiol were in the normal range (Table 1). During this time, a transabdominal pelvic ultrasound at the completion of menses demonstrated an endometrial thickness of 5.5–8.3 mm. Ovaries were present bilaterally and were described as normal. There was no comment regarding the presence of ovarian follicles. Fourteen days later, the endometrium was 8–10 mm thick, with echo characteristics of a secretory endometrium.

In April 1993, the patient developed hot flushes, lethargy, and amenorrhea. In May 1993, LH and FSH levels were elevated. Progesterone was at a nonluteal level, and the estradiol concentration was low (Table 1). PRL remained normal at 90 μIU/mL. Hormone replacement therapy was resumed in May 1993. Gonadotropin levels have remained elevated since that time.

Materials and Methods

Galactose-1-phosphate uridyl transferase deficiency was diagnosed at the Chemical Pathology Department of the University of Manchester on December 12, 1974, by Dr. V. Schwarz and was confirmed by Dr. J. Coakley of the Clinical Biochemistry Department at the Royal Alexandra Hospital for Children, Camperdown (Sydney, Australia), on November 11, 1993. In both cases, no enzyme activity was detected in red blood cell samples.

Before 1991, LH and FSH were measured in this patient at the Royal Alexandra Hospital for Children, Camperdown, using a time-resolved immunofluorescence method (Delfia, LKB Pharmacia, Oy, Torku, Finland). The normal range for prepubertal girls in this assay is shown in Table 1.

From 1991 on, LH and FSH were measured by an immunoradiometric assay (Bioclone, Marrickville, Australia). Progesterone was measured by a Diagnostic Product Corp. assay (Bio-Mediq Co., Box Hill, Australia). Estradiol was measured by a clinical assay format (Baxter Diagnostics Co., Murdoch Circuit, Brisbane, Australia). The normal range for these assays is shown in Table 1.

Received February 23, 1995. Revision received August 15, 1995. Rerevision received September 20, 1995. Accepted October 17, 1995.

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TABLE 1. The LH, FSH, estradiol (E_2), and progesterone (P_4) values together with concurrent therapy at various times

Normal range[a]	Date: 13–04-84 Age: 11 yr, 4 months	26–10-84 11 yr, 11 months	15–02-88 13 yr, 3 months	17–04-91 16 yr, 4 months	17–07-91 16 yr, 7 months	24–02-93 18 yr, 2 months	07–05-93 18 yr, 5 months
FSH (IU/L) 1.4–5.6, prepubertal girl 2–12, adult	6.9	9.5	29.0	63.4	65.1	3.4	38.1
LH (IU/L) 0.03–5.5, prepubertal girl 3–10, adult	0.5	<0.1	7.0	27.1	50.3	6.6	37.0
E_2 (pmol/L)		41	43		40	243	182
P_4 (nmol/L) 16–100				0.8		16	3.0
Therapy	Nil	Nil	Nil[b]	Ethinyl estradiol (10 μg/day)	Nil	Nil	Nil[c]

[a] The higher of follicular or luteal phase ranges are shown.
[b] Commenced ethinyl estradiol (10 μg/day) after this visit.
[c] Ethinyl estradiol and progesterone recommenced after this visit.

Discussion

Primary amenorrhea may be due to premature ovarian failure. Premature ovarian failure is diagnosed when a female less than 40 yr of age with amenorrhea has estrogen deficiency and elevated serum gonadotropin levels (1). It is reported to occur in approximately 1% of women in Western countries. There is no generally agreed gonadotropin threshold diagnostic of premature ovarian failure, but a firmer diagnosis is demonstrated by persistent (>1 yr) elevated gonadotropin levels (1). Premature ovarian failure has a variety of etiologies (1), including chromosomal abnormalities; history of surgery, chemotherapy, or radiation; autoimmune disease; and galactosemia (Table 2).

There are histopathological findings on ovarian biopsy that may correlate with various etiologies of premature ovarian failure. Afollicular ovaries and streak gonads are seen in chromosomal abnormalities with gonadal dysgenesis. A perifollicular lymphocytic infiltrate is described in autoimmune ovarian failure. Another subset of premature ovarian failure is the resistant ovary syndrome, first described in 1967 (2). In the resistant ovary syndrome, many primordial ovarian follicles are present at ovarian biopsy, consistent with the loss of ovarian sensitivity to gonadotropins.

Ovarian biopsy, particularly partial thickness biopsy at laparoscopy, is an imprecise method in determining ovarian histopathology (1). Findings in premature ovarian failure often vary throughout the ovarian tissue, and even multiple biopsies may miss focal lymphocytic infiltration or isolated sites where ovarian follicles exist. Moreover, the exact number of ovarian follicles at biopsy required to diagnose the resistant ovary syndrome has not been defined.

The resistant ovary syndrome may be diagnosed clinically when variable sensitivity to gonadotropins occurs over time: typically resistance with ovarian failure and high gonadotropin levels, followed by episodes of normal ovarian function.

In the diagnostic evaluation of patients with premature ovarian failure, associated clinical features may aid in identifying the etiology. There may be a history of pelvic surgery, irradiation, or chemotherapy. Physical examination may reveal dysmorphic features, such as those seen in Turner's syndrome, suggesting chromosomal abnormalities with gonadal dysgenesis. Intercurrent abnormalities, such as cataracts, cognitive deficiency, or hepatosplenomegaly, may suggest galactosemia, particularly when a family history exists. Evidence of other autoimmune endocrinopathies would suggest an autoimmune basis for the ovarian failure.

In the absence of a clear etiology, a karyotype to screen for recognized causes of gonadal dysgenesis should be requested. Usually, galactosemia will have been diagnosed earlier in life. However, particularly in primary amenorrhea, a red cell galactose-1-phosphate uridyl transferase test for galactosemia should be considered. Serum ovarian antibody tests for autoimmune ovarian failure vary among laboratories. We have not found this test to be useful.

We would not perform an ovarian biopsy to diagnose premature ovarian failure because it does not add to patient management and could be misleading. Intravaginal ultrasound may demonstrate ovarian follicles, consistent with the resistant ovary syndrome (3), but its precision and clinical utility remain undefined.

In our patient, the markedly elevated FSH levels were indicative of ovarian failure. The clinical course is consistent with the resistant ovary syndrome as the cause of premature ovarian failure. When first investigated, she was found to be hypogonadal with elevated gonadoptropin levels. Intermittent observation over almost 7 yr from the age of 11 yr showed a progressive elevation in gonadotropins consistent with premature ovarian failure, which was attributed to her galactosemia. The cyclical bleeding during treatment with a

TABLE 2. Premature ovarian failure: etiology

1. Autoimmune
   Including classic polyglandular syndrome types I and II
2. Chromosomal abnormalities
   45,XO ± Turner phenotype
   45,XO/46,XX, 45,XO/47,XXX, 45,XO/46,XX/47,XXX mosaics
   Familial and sporadic 46,XX variants including sensori-neural deafness and blepharophimosis
3. Postsurgical, postirradiation, postchemotherapy
4. Galactosemia
5. Idiopathic/unclassified (20–50% of cases)
6. Rare other
   Mumps
   Ovarian hemorrhage

constant dose of ethinyl estradiol (10 μg/day) was unusual and remains unexplained. During this therapy, gonadotropin levels were elevated, and progesterone was low on the one occasion that it was measured. After a period of combined estrogen and progesterone treatment, the patient had regular menstrual bleeding for almost 10 months. Ovarian biopsy was not performed, although the diagnosis of resistant ovary syndrome seems reasonable on both clinical and biochemical grounds.

Cases have been described in which patients with the apparent firm diagnosis of premature ovarian failure have subsequently been shown to ovulate, and in some cases, pregnancies have been recorded (1). The diagnosis of resistant ovary syndrome has been made in these cases. These reports and this case illustrate that premature ovarian failure is not an irreversible process.

No well controlled prospective trials have demonstrated the efficacy of any specific therapy in correcting premature ovarian failure. Glucocorticoid therapy in autoimmune ovarian failure and treatment with LH-releasing hormone agonists and antagonists (clomiphene and bromocriptine) in premature ovarian failure have not shown benefit in well controlled studies. In the resistant ovary syndrome, there are case reports and series suggesting that exogenous estrogen, particularly at pharmacological doses with gonadotropin suppression, may induce ovarian sensitivity to gonadotropins in some patients. Exogenous gonadotropins have been used after estrogen therapy (4). In this patient's case also, there was a temporal association of estrogen and progesterone use with the onset of regular menstrual bleeding.

Classical galactosemia is a rare inherited disorder of galactose metabolism due to a deficiency in the enzyme galactose-1-phosphate uridyl transferase (5). Premature ovarian failure commonly develops in females with galactosemia with either primary or secondary amenorrhea at presentation. In one large series (5), the prevalence of premature ovarian failure in females with galactosemia was 62%. The ovarian failure is usually irreversible, with atretic ovarian follicles (6). There are two other case reports of galactosemia with the resistant ovary syndrome (7, 8), although these were histopathological, rather than clinical, diagnoses. The pathogenesis of premature ovarian failure in galactosemia remains unclear. Proposed mechanisms include nonbioactive gonadotropins, blocking receptor antibodies, a receptor or postreceptor defect, or ovarian toxicity due to galactose metabolites (6).

Galactose-1-phosphate accumulates in the ovary both pre- and postnatally in galactosemic females and inhibits many biochemical pathways involved in carbohydrate metabolism. It has been proposed that the accumulation of phosphate results in the degradation of uridine nucleotides and cell death (5). There is no correlation between hypogonadism and circulating galactose levels, the time of onset and compliance with a lactose-free diet, or other organ damage in galactosemia (5). This may be due to local production of galactose-1-phosphate from glucose with local tissue concentrations greater than those predicted from systemic levels.

Recent evidence from hormone measurements in perimenopausal women show episodes of apparent ovarian failure with high gonadotropin levels, followed by normal menstrual cycles with normal gonadotropin levels, in a significant percentage of women (9). It seems reasonable to conclude that ovarian failure is not an absolute, but can be temporary and reversible. This temporary and reversible phase could be classified as a resistant ovary syndrome. Thus, it seems reasonable to postulate that progress through a resistant ovarian state is one of the pathways in the progression to irreversible ovarian failure (9).

In our case report, we clearly document a resistant ovary picture in a young patient with galactosemia, a condition usually associated with complete ovarian failure. The cause of ovarian failure in galactosemia and the menopause are likely to be different, yet they progress through a similar clinical pathway in at least some cases. This leads us to hypothesize that resistant ovary syndrome is one pathway in the progression to irreversible ovarian failure regardless of the mechanism. The resistant ovary syndrome then can be regarded as a marker of incipient irreversible ovarian failure. If correct, this has significant clinical implication in the assessment of patients with ovarian failure, because the resistant ovary syndrome may occur in up to one third of cases of premature ovarian failure (3) and one third of perimenopausal women (10). Women with the resistant ovary syndrome cannot be reassured that pregnancy is not possible if they wish to stop contraception. Alternately, if pregnancy is desired, perhaps therapeutic endeavors should not be delayed, although, as we have observed, there is no currently proven effective therapy to induce ovulation in these patients.

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