Premature Ovarian Failure

Abstract

The case histories of two patients are presented where ovarian failure with secondary amenorrhoea was successfully reversed using intravenous antibiotics. It is suggested that a bacterial infection could be the cause of ovarian failure and rising FSH and LH values in a subgroup of patients. All efforts should be made to identify these pathogens with proper culture studies and prompt therapy should be offered with broad-spectrum antibiotics.

Definition

Premature ovarian failure effects patients who are under 40 years of age. Typically, the menstrual period ceases without obvious genetic abnormalities. These patients exhibit amenorrhoea, elevated gonadotropin levels and subnormal estrogen levels with or without typical menopausal symptoms.[1]

Etiology

The exact etiology of this disease entity is unknown, but it is suggested that some patients might be born with a fewer than normal number of oocytes. On the other hand, some may exhibit excessive gonadotropic stimulation, thus the depletion of oocytes is accelerated.[2] These individuals have normal stature since the ovarian functions cease long after the epiphysis is closed. It is not uncommon to see patients with premature ovarian failure exhibiting auto-immune thyroiditis. In some patients, antibodies against gonadotropins have been described and some exhibit genetic mutations in the FSH receptor.[3]

Clinical Characteristics

Patients with premature ovarian failure represent a continuum of disease conditions. It has been observed that premature ovarian failure as a clinical manifestation is not necessarily a permanent state since a few patients resume normal or irregular ovulation and even pregnancies do occur. In some of the patients, menstruation was always irregular and some exhibited incomplete sexual development. As normal ovulation ceases, many of these women will develop typical menopausal hot flashes.

Blood Gonadotropin Levels

There is no uniform gonadotropin profile that would be characteristic for these patients. In many, typical post-menopausal FSH and LH levels are observed and, in others, the pituitary gonadotropins may fluctuate or are just slightly above the normal level.[4] One can see rising levels of LH or occasional LH surges followed by ovulation and a concomitant rise in blood Estradiol levels. Recent summaries on this disease condition conclude that rising levels of FSH by itself is no longer accepted as absolute evidence for ovarian failure. It is observed that

in some patients, ovarian failure may be a transient phenomenon and follicular activity can be observed with high frequency.

Evaluation of the Patients

Besides taking detailed clinical histories and performing careful physical evaluations, these patients should undergo serum calcium, phosphate and protein determination for the exclusion of often associated thyroid disease and thyroid antibody determination. In some, adrenal reserve should be assessed. In other patients, where gonadotropin resistance is documented, genetic evaluation may be justified for LH or FSH mutation.

Histological Evaluation of Ovarian Biopsies

Prior to the wide-spread use of transvaginal ultrasonography in evaluating ovarian structure, we routinely performed ovarian biopsies through laparoscopy. Typically, in these patients, we could not find follicular activities or corpora lutea, despite the fact that quite often follicles were present. Beneath the surface epithelium of the ovaries dense, hyalinized tissue was observed and most strikingly, in a number of cases we witnessed, lymphocytic and polymorphonuclear leukocytic infiltrates around follicles. These inflammatory cells were observed by others in the past and attributed to an auto-immune process, partially responsible for the ovarian failure. For us, these changes were suspicious of a microbial infection as the cause of the ovarian dysfunction.

Infectious Causes of Premature Ovarian Failure

We are presenting here two cases of secondary ovarian failures, where culture studies documented cervical, endometrial and ovarian infections with Chlamydia trachomatis or with anaerobic bacteria and where intravenous antibiotic therapy successfully restored cyclical ovarian function and ultimately, successful pregnancies were reported.

Case Report 1
Secondary amenorrhoea associated with Chlamydia trachomatis infection

A 39-year old white woman, gravida 11, para 2 (1 living), abortions 9, (1 induced), was initially seen because of secondary amenorrhoea in 1981. She wanted to become pregnant provided her endocrine problems could be resolved. An initial analysis of semen from her husband was normal: the sperm count was 88 million/ml, motility 3/60%, 75% oval forms. He had a history of gonorrhoea treated with intramuscular penicillin in 1956. His initial symptoms had promptly subsided but an episode of mild dysuria occurred a few weeks later and cleared spontaneously. His wife had used an intrauterine device at the time of the marriage when she was 26 years old and this was removed six months later when the couple decided to attempt a pregnancy. Between 1969 and 1979, she had had 11 pregnancies, the outcome of these is summarized in table 1. During these years she had had recurring vaginitis and bladder infections. At the same time, she noticed profound changes in her menstrual

pattern. The length of her menstrual bleeding, which had been five days with copious bright red blood, diminished to one day, and frequently only brownish staining occurred. Severe cramps that formerly characterized the first day of her menstruation had completely disappeared. In the 18 months before she was seen by us, she stopped having spontaneous periods and only responded to increasing dosages of clomiphene. In the six months before we saw her human menopausal gonadotropin (Pergonal) combined with human chorionic gonadotropin (HCG) were given. The patient stopped taking the Pergonal-HCG and had no periods for four months when she was first seen by us.

After the initial consultation medroxyprogesterone (Provera) 10 mg was given twice a day for five days. One day of brownish staining followed early in May, 1981. Hormone tests, performed 10 days later, included estradiol, follicle-stimulating hormone, luteinising hormone, and prolactin (table II). A progestereone assay was performed 10 days later. The tests were repeated a month later after a second Provera slough. Endometrial biopsies were performed 17 days after the Provera treatment (fig 1a). The husband's seminal fluid and the endometrial biopsy specimens were cultured for *Mycoplasma* spp, aerobic and anaerobic bacteria and Chlamydia trachomatis (table 11). In June 1981, a diagnostic laparoscopy and biopsy of the ovaries were performed. Through the laparoscope both ovaries appeared pearly white and had a rubbery consistency with no sign of recent ovulation or a corpus luteum. Several corpora albicantea were present. Both tubes were patent, the uterus and other pelvic structures appeared normal and there was no gross evidence of infection. The ovarian biopsy specimen was examined histologically and a portion of tissue was cultured for *Mycoplasma* spp, aerobic and anaerobic bacteria, and *Chlamydia trachomatis*. The only organism isolated was Chlamydia trachomatis. Both the woman and her husband were then treated with doxycycline (table 11); the patient received intravenous doxycycline 100 mg twice daily for six days followed by 100 mg P.O. twice a day for three weeks as an outpatient; the husband received 100 mg P.O. twice daily for 30 days. The patient resumed spontaneous menstruation in July 1981, and repeat hormone studies and endometrial biopsies were performed in July and August (table 11). Culture for *Chlamydia trachomatis* was repeated on the endometrial biopsy and the seminal fluid and produced no growth (table 11). Her last menstrual period began on 11 October 1981, and a beta-subunit assay performed on 16 December 1981 confirmed the presence of an intrauterine gestation, which was compatible with the dates. At the end of June 1982, the patient delivered a healthy female infant.

Table 1 Outcome of 11 pregnancies before the doxycycline treatment

Pregnancy	Date	Gestation (weeks)	Fetal maternal outcome	Diagnostic procedures and treatments
1	1969	28	Premature rupture of membranes, neonatal death	
2	1970	12	Spontaneous abortion	Endometrial biopsy showing luteal-phase defect, normal serum progesterone
3	1970	16	Spontaneous abortion	Progesterone + prednisone, normal HSG
4	1971	37	Premature rupture of membranes, live male, endomyometritis	Conception after a 10-day tetracycline course for dermatological condition, ampicillin and cephalotin intravenously for postpartum endomyometritis

5	1972	6	Induced abortion	
6	1975	17	Incompetent cervix, spontaneous abortion	Advised for cerclage, normal karyotype
7	1976	11	Spontaneous abortion	Endometrial biopsy and serum progesterone, show luteal-phase defect, increasing doses of clomiphene
8	1977	12	Spontaneous abortion	
9	1978	8	Spontaneous abortion (followed by dilatation and curettage)	
10	1979	7 days	Spontaneous abortion	Beta-subunit
11	1979	11 days	Spontaneous abortion	Beta-subunit

HSG = Hysterosalpingogram

Table 11

Culture results				Hormones				
Date	Seminal Fluid	Endometrial Biopsy	Ovarian Biopsy	FSH (miu/ml)	LH (miu/ml)	Prolactin (ng/ml)	Estradiol (pg/ml)	Progesterone (ng/ml)
Before doxycycline treatment:								
May 1981	+	+		12	15	11	108	0.4
June 1981	+		+	11	14	15	96	0.64
After doxycycline treatment:								
July 1981	-	-		7	13	5	475	21.0
August 1981	-	-		10	11	4	392	10.0

+ = positive; - = negative, FSH = follicle-stimulating hormone; LH = luteinising hormone

Case Report 2
Secondary amenorrhoea associated with anaerobic bacteria

E.S. was referred to me in September 1995 with a rather stunning menstrual history. She experienced her first menstrual period at age twelve and was regular until her college years when the periods gradually became more and more irregular, skipping one and then eventually two to three month periods. The first change in her menstrual period occurred shortly after Ms. S. became sexually active. By age 20, her periods completely ceased. A birth control pill regimen was instituted to keep her menstruation regular. At age 23, Ms. S. married, but after a complicated and frustrating infertility workup and treatment regimen, including fertility drugs and varying procedures without a successful pregnancy, she now age 32 divorced her husband.

From 1988 on, she progressively suffered from hair loss, depression, lack of sexual interest and gradually progressing osteoporosis. A year prior to her visit to our office, estrogen patches were given, which were switched to Demulen birth control pills and when the menstruation completely ceased, she stopped all hormonal preparations. At the time of her visit to my office, she was on Zoloft and Elavil maintenance therapy. She appeared emaciated; her height was 5'2'' and she weighed 98 lbs. My examination was essentially negative and, as is routine, culture studies were performed, which yielded a few Group B Streptococcus and E Coli, two aerobic bacteria in the cervical area. The uterine biopsy was positive for two

Clostridia: innocuum and bifermentans. Her Mycoplasma, Chlamydia and yeast cultures were negative.

An office sonogram revealed a normal appearing uterus as well as both ovaries with a number of follicles present. A blood test for pituitary hormones revealed FSH 6.1 miu/ml, LH 4.9 miu/ml and Estradiol 57 pg/ml. Empirically, I offered the patient ten days of Augmentin, 500 mg, TID. She reported a spontaneous period a month after completing the course of Augmentin.

A repeat culture, from November 1995, revealed many E Coli, many yeast colonies in the cervical area and from the endometrial biopsy, a Propionibacterium was recovered. The patient exhibited normal periods until February 1996. From then on, she failed to bleed spontaneously.

In April 1996, I offered the patient a ten-day intravenous Clindamycin therapy regimen, which she completed on April 18, 1996. Following the completion of the intravenous course, the patient spontaneously resumed menstruation and established a normal pattern, all through 1997 and 1998. Her only complaints remaining were premenstrual tension symptoms, which were gradually improving during 1998.

Two bone density studies were obtained. One was performed in January 1996 revealed severe osteoporosis present in the spine and femoral neck areas. The other was performed in February 1997 following a year of Fosamax therapy, when the readings were interpreted as significantly improved and just osteopenic.

In the middle of 1998, Ms. S. married for the second time and a birth announcement of a full-term, male infant born on November 17, 1999, weighing 7 lbs ¾ ounces is the final note in the chart.

The two case histories clearly present a sub-group of women with premature ovarian failure where an infectious organisms readily identified and readily treated is the cause of the disease condition. Since these two patients, scores of others have been treated with antibiotics successfully to normalize ovarian function or to reverse rising FSH and LH levels, especially in patients who are undergoing complex infertility therapies and ART procedures. In recent years, we stopped performing routine ovarian biopsies and our treatment recommendations are based on a synthesis of careful history, serum hormone evaluation, cervical, endometrial biopsy culture and seminal fluid culture results as well as transvaginal ultrasound evaluation of the ovarian structures.

Whenever the history is suspicious for premature ovarian failure associated with a reproductive event combined with borderline or slightly elevated FSH and LH values, we base our antibiotic recommendation on culture studies obtained from cervical, endometrial and the male partner's seminal fluid.

It is not only the presence of Chlamydia trachomatis that prompts our recommendation for antibiotic therapy. Successful normalization of menstrual cycle was achieved after documentation of unusually heavy or an unusual combination of anaerobic bacteria within the uterine biopsy and/or cervical/seminal fluid cultures. We are more hopeful in predicting favorable post-antibiotic therapy outcome if and when a sonography of the ovaries revealed numerous, inactive follicles. A routine test dose of three weeks of Doxycycline, 100 mg BID, is given first to explore the potential beneficial effect of antibiotics. If and when a significant drop in the post therapy FSH/LH level is documented with a concomitant rise of serum Estradiol, following a sensitivity report on the culture studies, an immediate intravenous antibiotic therapy is initiated using broad-spectrum antibiotics. This therapy protocol was followed with success, not only in patients where complete premature ovarian failure was documented, but in quite a few of those who were rejected from further fertility procedures or ART centers because of rising gonadotropins. If there is a high degree of suspicion for the presence of a pelvic inflammatory disease accompanying the premature ovarian failure, we bypass the oral Doxycycline therapy and immediately recommend intravenous antibiotics.

Our second case clearly documents the far-reaching consequences of premature ovarian failure in causing bone loss and its negative affect on female sexuality. We firmly believe that the giving of ever-increasing doses of gonadotropins in this subgroup of patients is clearly detrimental and rapidly accelerates a process that is fully reversible in its early stage.

References

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