Secondary amenorrhea despite normal endometrial development with secretory changes and absence of uterine synechiae – a second case of the endometrial compaction – apoptosis syndrome

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Summary

Purpose: To report the second case of amenorrhea related to endometrial compaction apoptosis syndrome. *Materials and Methods:* A female with secondary amenorrhea was evaluated with sonography, hysteroscopy, serum estradiol and progesterone levels, serum luteinizing hormone (LH), follicle stimulating hormone (FSH), and endometrial biopsy. *Results:* Initially she was found to be ovulatory. However she did not menstruate despite the development of adequate endometrial thickness and a normal secretory endometrial biopsy. Hysterosalpingogram failed to detect synechial. Subsequently she developed hypogonadotropic hypogonadism, but she still failed to menstruate despite estrogen followed by progesterone. *Conclusions*: Amenorrhea can occur despite secretory endometrial changes without a uterine abnormality.

Key words: Amenorrhea; Normal uterine cavity; Endometrial compaction; Endometrial apoptosis.

Introduction

Amenorrhea in the presence of normal estrogen, either with normal ovulation or failure to menstruate despite withdrawal of exogenous progesterone, is usually secondary to endometrial synechiae, i.e., Asherman's syndrome.

However, there are rare cases in humans where despite the production of adequate estrogen without evidence of uterine synechiae, menstruation does not occur [1]. In the aforementioned case, the woman ovulated as evidenced by a rise in serum progesterone and even had a normal luteal phase endometrial biopsy, but no menses. Hysteroscopy was normal [1].

Some animals, such as rabbits, sheep, and hamsters have hypertrophy and degeneration of uterine luminal epithelium in response to estrogen and progestins; however they do not menstruate but undergo a process of cell destruction by apoptosis [2]. These animals lack the spiral arterioles that are responsible for menstrual flow in primates [2]. Thus the aforementioned case may have a situation analogous to rabbits, sheep, and hamsters.

Indeed histological studies in the human species concluded that the marked reduction in endometrial thickness from the immediate pre-ovulation state to shortly post-menstruation may be primarily due to loss of fluid and the result of apoptosis of the spongy layer [3]. Another study in humans concluded that in most cases, an appreciable fraction of the stratum spongiosum actually disintegrates but endometrial tissue superficial to the basal layer remains in situ at the end of menstruation [4]. Very heavy vs. very light menses (or no menses) in ovulating women may be thus related to the extent of endometrial shedding [4].

A review of the literature found no new articles with similar findings (normal ovulation but amenorrhea without a known uterine factor e.g., obstruction to outflow or intrauterine adhesions). Another case of apparent endometrial apoptosis or compaction without shedding is now reported.

Case Report

A 22-year-old female consulted us because of a history of primary amenorrhea, despite normal sexual development at the appropriate age. Amenorrhea occurred despite documented normal ovulation at the age of 17, as evidenced by both serum progesterone and endometrial biopsy. Ultrasounds showed a normal uterine cavity with endometrial thickness reaching 10-12 mm.

More evidence of folliculogenesis was the fact that she had a tendency to develop ovarian cysts and had five laparoscopes to remove ovarian cysts. When she presented at the age of 22, she wanted to know the nature of her problem and to determine if pregnancy was possible. She added that a recent attempt to stimulate her to ovulate with gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH) combination failed to stimulate folliculogenesis.

The following serum studies were obtained: low estradiol - < 10 pg/ml, low FSH of < 0.7 mIU/ml, low LH < 0.2 mIU/ml, cor-

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tisol 25.3 mcg/dl (normal 4.0-22.0 mcg/dl), dehydroepiandrosterone sulfate – 185 mcg/dl (normal 45-320 mcg/dl), free thyroxine 1.0 ng/dl (normal 0.8-1.8 ng/dl), thyroid stimulating hormone 2.36 mIU/l (normal < 2.5 mIU/l), and prolactin 20.9 ng/ml (normal 2-20.0 ng/ml).

A pelvic sonogram revealed the right ovary to measure 16 x 17 x 16 mm and the left one to measure 21 x 19 x 22 mm. No antral sized follicles were seen and only a few pre-antral sized ones of two to three mm were noted.

With six mg/day of estradiol for 18 days, she developed a 14-mm endometrial thickness. She continued the estradiol while adding 10 mg medroxyprogesterone acetate for 14 days, however menses did not ensue.

Her endometrial echo pattern immediately prior to starting progesterone was triple-line and one week later on progesterone converted to the appropriate homogeneous hyperechogenic pattern [5, 6].

Discussion

Though her estrogen deficiency related to her apparent isolated gonadotropin deficiency (but not related to significant hyperprolactinemia) would result in amenorrhea, her development of secondary amenorrhea despite previous ovulation with no apparent uterine synechiae is consistent with the diagnosis of endometrial compaction – apoptosis syndrome that has only been reported once before [1]. Further confirmation was her failure to menstruate despite high-dosage estrogen followed by progestins which allowed endometrial proliferation but no shedding. Evidence that this problem is not related to progesterone receptor deficiency or inadequacy was excluded by the development of a secretory endometrium.

Her failure to ovulate despite a course of exogenous gonadotropins including LH and FSH could have two possible explanations. Sometimes, hypogonadotropic hypogonadism needs a prolonged course of exposure to gonadotropins in high-dosage before a response is seen even with estrogen priming. With no insurance coverage for these expensive drugs and failure to show a typical response to a moderate dosage, the therapy was discontinued. Sometimes this resistance may be related to associated growth hormone deficiency and the addition of growth hormone can allow response to less gonadotropins, but eventually with a high enough dosage and time of exposure, one will typically see a response [7]. Unfortunately though the young woman wanted to conceive, she would have to wait until she acquired the needed funds or the needed insurance coverage.

The question arises as to whether conception is even possible (the first case report chose not to try to conceive since her husband had a vasectomy). This author has seen one previous case of secondary amenorrhea related to endometrial compaction – apoptosis syndrome (unreported) and she did in fact have a successful pregnancy.

In the present case, it is possible that the multiple ovarian surgeries have damaged the ovaries and she would have shown an increased serum FSH related to diminished oocyte reserve, if there had not developed an independent hypothalamic pituitary problem. Thus, the frustrating thing for the patient without insurance is that there is no guarantee that following high-dose exogenous gonadotropins that she will even respond. It is interesting that in another case of amenorrhea related to a uterine defect, i.e., congenital absence of the uterus, which is usually associated with normal estrogen and ovulation, she also had accompanying hypogonadotropic hypogonadism [8].

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