Secondary amenorrhea with normal ovulatory cycles in a young virgin with normal follicle stimulating hormone levels – a case report

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Summary

Purpose: To determine if normal ovulation is possible despite amenorrhea in the absence of any obvious uterine abnormalities or adhesions. *Methods:* The study was conducted on a 17-year-old virgin with normal sexual development and normal secondary sexual characteristics whose menarche was at age 12 but whose menses ceased after two menstruations. She was first treated with medroxyprogesterone acetate 10 mg x ten days and then a cycle of oral contraceptives. *Results:* She failed to get menses following progesterone (P) withdrawal and following a cycle of oral contraceptives. All of her pituitary function studies were normal. Her serum follicle stimulating hormone (FSH) was 3 mIU/ml, luteinizing hormone (LH) 9 mIU/ml, estradiol (E2) was 107 pg/ml and the serum P was 3.9 ng/ml. These values were consistent with recent ovulation. However menses failed to ensue. *Conclusions:* This case confirms that in humans, similar to some non-primates, ovulation is possible without shedding the endometrium. Possibly she lacked spiral arterioles similar to ovulating mammals. Her *virginal* introitus and lack of any serious febrile illness made Asherman's syndrome highly unlikely. Her normal menstrual cycle at age 12 not only excluded a mullerian abnormality or imperforate hymen but led to speculation as to whether anovulatory bleeding from unopposed estrogen was possible but that somehow the presence of P inhibited the endometrial shedding process. In contrast to a previously reported study, this young woman almost had primary amenorrhea whereas the former case had more menses during her life but they ceased shortly after age 30.

Key words: Secondary amenorrhea; Ovulation; Normal uterus.

Introduction

Some animals, e.g., rabbits, sheep, and hamsters have hypertrophy of the luminal epithelium in response to estrogen followed by degeneration of the epithelium in response to estrogen and progesterone (P) exposure [1]. However, they do no menstruate because the atrophy of the endometrium is completely related to apoptosis of the cells [1]. From a histologic standpoint these animals lack the spiral anterioles that are responsible for the menstrual flow in primates.

A previous case was described of a 35-year-old woman who had developed secondary amenorrhea four years prior and in the year before treatment had only three episodes of "spotting" for two hours [2]. Her evaluation revealed that she was having evidence of normal ovulation but no menses. Hysteroscopy showed no evidence of scar tissue and she gave no history of any previous surgical procedures of the uterus or uterine cavity, or pelvic infections. Artificial estrogen followed by progestin therapy failed to induce menses. There was evidence that she had normal estrogen and progesterone receptors in the endometrium because an endometrial biopsy taken seven days after ovulation showed appropriate secretory changes [2]. The exact mechanism of why she developed secondary amenorrhea was not known but it was pondered whether it had something to do with fewer ovarian follicles since she was documented to have elevated serum follicle stimulating hormone (FSH) when the serum estradiol (E2) was < 50 pg/ml on three separate occasions [2]. In fact, she had been misdiagnosed by another physician as having premature menopause.

We present another case of secondary amenorrhea but in this case the secondary amenorrhea developed in a teenager with normal serum FSH and after having only two menstrual periods, which were most likely anovulatory.

Case Report

A 17-year-old female presented with secondary amenorrhea. She had normal sexual development and her menarche had started at age 12. After her very first menstrual cycle she had another one a month later but no menses since that time.

There was a lot of family stress at that time so her lack of menses over the next several years was attributed to a psychogenic amenorrhea from anovulation. However at age 17 she was given medroxyprogesterone acetate for ten days but she failed to get her menses with the withdrawal of the drug. A cycle of oral contraceptives with 35 μg of ethinyl estradiol also failed to induce menses.

She was then referred for evaluation. Upon examination there was a *virginal* introitus and she preferred to forego a pelvic examination or ultrasound. She did have adult-type secondary sexual characteristics. The following serum hormonal evaluations were obtained to check her pituitary functions: free thy-

Revised manuscript accepted for publication May 7, 2007

roxin (T4) – 1.10 ng/dl (nl 0.83 to 1.44), thyroid stimulating hormone (TSH) – 0.92 uIU/ml (nl – 0.360 to 5.8), cortisol – 9.9 ug/dl (nl – 3.1 to 22.4) and her prolactin level was 18.8 ng/ml (nl 2.8 to 29.2).

She denied having monthly menses and any monthly abdominal pain or abdominal pain in general. Her serum E2 on the day of evaluation was 107 pg/ml, serum P was 3.9 ng/ml, serum FSH was 3 mIU/ml and her LH was 9 mIU/ml. These values were consistent with recent ovulation. However she once again failed to get spontaneous menses.

A repeat of her serum E2 and P and FSH taken 18 days later found a serum E2 of 47 pg/ml, P of 0.2 ng/ml, and the serum FSH was 3 mIU/ml.

Discussion

In a search of the world literature we could not find another case of amenorrhea despite ovulation and absence of Asherman's syndrome since the one published in 1989 [2].

Though the first case was better studied including hysteroscopy and endometrial biopsy it left a few questions. One was whether this phenomenon could somehow be related to the decrease in egg reserve in the previous case as manifested by a high serum FSH.

In contrast this teenager had a perfectly normal serum FSH when the serum E2 was low. Sometimes a woman can have a heterophile antibody leading to a false increase in serum hormonal levels but this was not the case since her serum P dropped down to 0.2 ng/ml [3].

The first two periods of a young woman's life are generally anovulatory. Clearly nothing happened from a physical standpoint to this young virgin, e.g., pelvic infection, undisclosed therapeutic abortion, D&C, etc. Whether the initiation of ovulation and the type of histologic changes that occur may provide a clue to this strange condition remains to be seen. This case is much closer to being the first report of primary amenorrhea despite normal ovulation in the absence of endometrial adhesions or mullerian abnormalities. The fact that she did have two spontaneous menses at age 12 and does not have abdominal distention or cyclical abdominal pain fairly well excludes mullerian dysgenesis or an imperforate hymen.

Her history raises the question as to whether breakthrough bleeding by continuous estrogen exposure might be possible but that somehow changes induced by the progesterone thwart shedding of the stratum functionalis.

To prove that ovulatory amenorrhea is not due to the loss or down-regulation of estrogen and progesterone receptors could be easily determined in a non-invasive manner via ultrasound, by watching the endometrium thicken (an estrogen-related event) and then looking for the architectural changes induced by P (homogeneous hyperechogenic pattern) in the mid-luteal phase [4, 5]. Admittedly it would be best accomplished by transvaginal ultrasound which would not be possible because of her virgin status, but we thought possibly transabdominal sonography might also give us this information. However, the patient preferred not to even attempt this by transabdominal ultrasound at the time because of a previous traumatic experience [4, 5].

Bartelmez concluded that a marked reduction in the thickness of the endometrium is primarily due to loss of fluid and the resulting collapse of the corpus spongiosum [6]. McLennan and Rydell 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 [7]. They also concluded that endometrial tissue shedding is less extensive than many believe it to be and that the amount of shedding varies widely from one uterus to another [7].

It could be speculated that for some reason this young woman lacks spiral arterioles similar to non-primates and thus does not get a menstrual flow. However these animals are fertile. It remains to be seen in the future if this lack of endometrial shedding will be associated with infertility or not.

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