Original Articles

Reproductive Biology Section

Failure to have menses following progesterone withdrawal in a normal estrogenic woman with polycystic ovarian syndrome who menstruates with oral contraceptives

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Summary

Purpose: To evaluate a case of a normal estrogenic woman with amenorrhea and polycystic ovarian syndrome who fails to get menses after progesterone withdrawal but who menstruates with oral contraceptives. *Methods:* The following sera assays were obtained: total testosterone (T), free T, weakly bound T, dehydroepiandrosterone sulfate, 17 hydroxyprogesterone, estradiol, free thyroxin, thyroid stimulating hormone, prolactin, evening cortisol, LH and FSH. *Results:* The total testosterone was markedly elevated but the free testosterone was normal and the free and weakly bound testosterone was the high end of normal. The LH/FSH ratio was markedly increased consistent with the ultrasound findings of polycystic ovarian syndrome. Vaginal cytology showed a mixed high estrogen/high androgen effect and the endometrial thickness was only 5 mm. Twice she failed to have menses following progesterone withdrawal. *Conclusions:* One hypothesized mechanism is that the high testosterone levels even though mostly in the bound form inhibited estrogen from causing adequate endometrial development.

Key words: Progesterone withdrawal; Amenorrhea; Endometrial thickness; Polycystic ovarian syndrome; Testosterone.

Introduction

The classic dogma concerning polycystic ovarian syndrome (POS) is that women with POS are hyperestrous, tend to form thicker endometria because of lack of progesterone opposition and are more prone to endometrial hyperplasia. Some clinicians suggest that when faced with a woman with amenorrhea and clinical symptoms and signs of androgen excess a progesterone withdrawal test should be performed and if menses ensue the woman probably has POS. To be sure that a 21 hydroxylase type of congenital adrenal hyperplasia does not exist, a serum 17 hydroxyprogesterone level could be drawn and if normal the diagnosis would be POS.

If a woman with apparent polycystic ovaries does not achieve menses following progesterone withdrawal then she could be pregnant or have some problem with the endometrium, e.g., intrauterine adhesions (Asherman's syndrome).

A case is described of a woman with normal estrogen who was not pregnant, never had an intrauterine procedure, and did show a normal uterine component by having menses while using oral contraceptives, and yet failed to get menses after progesterone withdrawal. A theory will be presented to explain this apparent paradox.

Case Report

A 30-year-old woman who was five feet tall and weighed 112 pounds presented with secondary amenorrhea. She was diagnosed as having POS based on the classic appearance on pelvic sonography and increased serum androgen levels. Her referring physician had obtained the following serum levels: serum testosterone 137 ng/dl (nl 20-76 ng/dl) and serum estradiol 105 pg/ml. Furthermore, she did not have insulin resistance as evidenced by her glucose level of 85 mg/dl with a serum insulin level of < 2 uIU/ml) (nl = 0-29.1 uIU/ml). She had the classic increased LH/FSH ratio with LH = 15.8 mIU/ml and the serum FSH was 2.9 mIU/ml. Serum prolactin was normal at 5.6 ng/ml.

Clinically, besides the amenorrhea for one and a half years, she only had mild hirsutism of the upper lips with no other androgen excess symptoms or signs.

The woman had failed to have withdrawal menses two times with 10 mg medroxyprogesterone acetate for 12 days. Repeat testing revealed a total serum testosterone (T) of 141 ng/dl, sex hormone binding globulin of 85 nmol/l (nl - 14 to 102 nmol/l, serum-free testosterone of 14 pg/ml (nl - 1-21pg/ml), serum testosterone free and weakly bound of 29 ng/dl (nl = 3-29 ng/dl), serum LH of 22.3 mIU/ml and serum FSH of 4.4 mIU/ml, a serum 17 hydroxyprogesterone level of 189 ng/dl (normal follicular phase 185 or less), dehydroepiandrosterone (DHEA) sulfate level of 131 mcg/dl (nl - 40-325 mcg/dl), a serum beta hCG level of < 2 mIU/ml, and a pm cortisol of 5.0 mcg/dl (normal for time taken 3.0-17 mcg/dl). Her free thyroxin and thyroid stimulating hormone levels were normal.

The woman was not trying to conceive and previously had stopped oral contraceptives because of side-effects. Since she had only minimal clinical manifestations of her markedly elevated serum testosterone (T) she elected not to do anything

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about the elevated level. She was advised to recheck the T level in four months since a rapidly rising level could increase suspicion of a T-secreting ovarian or adrenal neoplasm possibly causing a polycystic ovarian state [1, 2]. Since she was producing adequate estrogen she was advised not to take estrogen replacement. Furthermore since the ultrasound showed in addition to the classic polycystic ovary appearance (right ovary measured 33 x 42 x 37 mm and left ovary 53 x 78 x 56 mm with multiple follicles about 6 mm in a pearl necklace pattern) that she only had a 5 mm endometrium, she was advised not to take supplemental progesterone for unopposed estrogen as is the typical suggestion for POS.

Her vaginal cytology showed the classic mixed hormonal effect, i.e., superficial cells and parabasal cells seen together on the same slide, thus showing a high estrogen effect and high androgen effect.

Discussion

It is not clear why despite the very high serum testosterone (higher than most women with POS) the serum free testosterone was quite normal. The active hormones are considered the free and weakly bound T and that level was the high end of normal.

The normal free and the top normal free and weakly bound T could explain the lack of clinical androgen clinical manifestation other than very mild hirsutism of the upper lip but does not explain the reason for the high total T since the sex hormone binding globulin level was normal.

If there was a high level of active T it could be hypothesized that testosterone competes with estrogen in stimulating the growth of the endometrium. However the free T was completely normal. The possibility exists that although the bound T is not considered to be a major factor in hirsutism, acne and alopecia, it may still be very active in acting to compete with estrogen in the genitourinary tract. This would also explain why despite the absence of hyperandrogen characteristics there was a marked androgen effect seen on vaginal cytology. The mixed hormonal effect seen on vaginal cytology is usually only found with severe hyperandrogen states.

Another possible explanation is that this woman fortuitously had a paucity of receptors in the hair follicles and skin for dihydrotestosterone to explain the absence of hirsutism, acne or alopecia. The explanation for the normal free T level could be laboratory error for the free T assay but not for the total T assay.

Whichever theory is operational in this woman, this case demonstrates that one cause of failure to have menses following a challenge with progesterone withdrawal in a woman with normal estrogen could be high levels of testosterone competing with estrogen leading to a thinned endometrial lining. The analogy is similar to the inhibition of menses by combining daily conjugated estrogen replacement in menopausal women with a small daily dosage of medroxyprogesteorne acetate or newly developed oral contraceptives that lead to poor endometrial development and lack of menstrual shedding by daily consumption of a pharmacologic higher level of estrogen than is normally made with a potent 19-nor testosterone derived progestin.

The question arises that if this hypothesis of high androgen levels interfering with endometrial development is correct why did this woman have adequate menses while on the oral contraceptives? The possibility exists that by the oral contraceptive suppressing pituitary LH the testosterone levels were suppressed while taking the oral contraceptive and thus did not compete with estrogen in causing endometrial proliferation.

Based on these observations and hypothesis the woman was advised that when she is ready to conceive it may be necessary to find an oral contraceptive that she can tolerate to lower the androgen levels before starting follicular maturation drugs to induce ovulation to allow adequate endometrial development. Alternatively, she could be pretreated with a GnRH agonist with replacement estrogen therapy.

Generally, when such high levels of total T are generated with polycystic ovaries, hyperthecosis and marked insulin resistance are present. This patient clearly did not even have a trend for insulin resistance. Though this very high testosterone level was obtained twice two months apart, drawn from two different offices, the blood was sent to the same commercial laboratory. Thus the possibility exists that the free and weakly bound T levels were accurate but the total T was falsely high. In this case it could be hypothesized that the endometrium of some women may be markedly sensitive to even top normal free plus loosely bound testosterone thus inhibiting endometrial development.

References

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