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Case Report

Can Adrenal Progesterone Assist in the Maturation of the Endometrial Lining and Regulation of Menses in Turner Syndrome?

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Abstract

Background: In Turner syndrome with primary ovarian failure, low-dose estrogen is started to induce puberty. Progesterone is added after breakthrough bleeding or after 2 years. In primary ovarian failure, the only source of progesterone is adrenal.

Case: A girl with Turner syndrome (45X) had primary ovarian failure since infancy. At 12 years, puberty was induced with transdermal estradiol. At 14.2 yrs, she had Tanner 3 breasts and 3 irregular periods, becoming regular with normal flow only on transdermal estradiol. Weekly serum progesterone was detectable. ACTH stimulation test increased serum progesterone from 0.27 to 1.68ng/mL at 60 mins. Regular menses continued for 16 months on transdermal estradiol without progesterone replacement.

Conclusion: Rarely, patients with Turner syndrome and primary ovarian failure experience regular menses on transdermal estradiol without progesterone replacement. Adrenal progesterone may play a role.

Keywords: Adrenal Progesterone; Turner syndrome; Estrogen

Introduction

Turner syndrome (TS) can be due to 45, X monosomy, 45, X/46,XX mosaicism, or a structurally abnormal X chromosome. Individuals typically have what has been described as streak ovaries, i.e., ovaries consisting primarily of connective tissue and very few follicles. Primary ovarian failure (POF) is a well-described characteristic in this population.

In TS with POF, low-dose estrogen therapy is started at 11-12 years of age, with dose increments over 2-3 years. Progesterone is added once breakthrough bleeding occurs or after 2 years of estrogen treatment. Irregular bleeding can occur from unopposed estrogen but both exogenous estrogen and progesterone are necessary for regular menses. In POF, the only source of endogenous progesterone is adrenal. Adrenal steroidogenesis has been postulated to play a role in progesterone increase during the menstrual cycle, and LH receptors have been found in the adrenal cortex. [1]

We report a case of primary ovarian insufficiency due to Turner Syndrome in which estrogen replacement therapy resulted in regular menstrual periods despite the lack of exogenous progesterone replacement. We hypothesize that adrenal progesterone production may have played a role in this patient's menstrual cycles.

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Case

An adolescent girl with Turner Syndrome (45X) was diagnosed with primary ovarian failure at 1 month of age. Follicle stimulating hormone (FSH) was 65.66 U/L and luteinizing hormone (LH) 8.31 U/L. At 12 years, besides TS stigmata, she had prepubertal breasts and sparse, thin pubic hair with high FSH 88.2 U/L and LH 20.13 U/L.

Pubertal induction with transdermal estradiol (TDE) patch was started at 6.25 mcg twice a week with dose increments up to 25 mcg twice a week over the next 2 years. At 14.2 years, she had Tanner 3 breasts and pubic hair and started menarche. She had 3 irregular periods over the next 6 months. At 14.8 years, menses started occurring regularly only on exogenous TDE (FSH 11.3 U/L, LH 5.92 U/L, E 37 pg/mL). Each period would last 3 to 4 days with regular flow. At 15 years, weekly serum progesterone on day 15 after her last menstrual period (LMP) showed consistently detectable levels of 0.5, 0.6, 0.7, and 0.6 ng/mL respectively (reference range: follicular phase 0.15-1.4, luteal phase 3.3-25.5, mid-luteal phase 4.4-28, post-menopausal <0.5; however both adrenal and ovarian sources of progesterone are included in these reference ranges; no normative data was found on reference ranges for adrenal progesterone alone) (Table 1).

Cosyntropin stimulation test showed an increase in serum cortisol from 5.2 to 28.5 mcg/dL and serum progesterone from 0.27 to 1.68 ng/mL at 60 minutes (Table 2). An ultrasound study showed a uterine size of 5.7 x 1.8 x 3.5 cm and endometrial stripe 11 mm. The ovaries were not visualized. Anti-Mullerian hormone (AMH) was <0.015 ng/mL and inhibin B <10 pg/mL, consistent with no ovarian function. Menses continued at regular intervals

Table 1: Gonadotropin, estradiol, progesterone, DHEA-S levels and pelvic US.

Age (yrs)	Number of days since last period	Estradiol patch (mcg)	Period	LH (U/L)	FSH (U/L)	Estradiol Ultra-sensitive (pg/mL)	Progesterone (ng/mL)	DHEA-S (ug/dL)	Uterine size (cm)	Ovarian volumes (right ovary, left ovary)	Endometrial stripe
0.2				8.31	65.66						
9				4.09	40.8	<2					
10.8									1.5 x 0.5 x 1.1	not visualized	not visualized
11.2				14.73	87.1						
11.8				20.13	88.2			163			
12		6.25									
12.2		6.25				<2					
12.7		12.5									
13.4		12.5		8.83	53	26					
14		12.5				13		169			
14		25									
14.2		25	X								
14.25	33	25		4.18	23.7	64					
14.3	68	25	X								
14.4	31	25	X								
14.75	85	25	X								
14.8	28	25		5.92	11.3	37	0.55	198			
14.8	36	25	X								
14.9	20	25							5.7 x 1.8 x 3.5	not visualized	11 mm
14.9	26	25	X								
15	15	25					0.5				
15	21	25					0.6				
15	28	25					0.7				
15	35	25					0.6				
15	36	25	X								
15.1	25	25	X								
15.2	22	25	X								
15.25	40	25	X								
15.3	29	25	X								
15.4	23	25	X	1.6	6.2	62		145			
15.5	26	25	X								
15.5	22	25	X								
15.8	43	25	X	4.33	10.5	67	0.64	162	4.2 x 2.5 x 3.6	not visualized	9 mm
15.9	41	25	X	1.63	7.3		0.67	174	4.3 x 2 x 3.3	not visualized	10 mm
16	37	25	X								
16.1	49	25	X								
16.2	29	25	X								
16.25	10	25		2.97	9.4	46	0.56				

Table 2: ACTH stimulation test done on day 20 post-LMP.		
	Cortisol (mcg/dL)	**Progesterone (ng/mL)**
Baseline	5.2	0.27
60 mins after cosyntropin 250 mcg IV	28.5	1.68

of 22-49 days for 13 months on TDE without progesterone replacement. However, since ultrasound studies done 3-4 days after onset of bleeding showed that the endometrial lining does not fully shed with these bleeding episodes, a decision was made to start the patient on 10 days of oral progesterone every 3 months.

Discussion

The menstrual cycle is divided into a preovulatory follicular phase, a postovulatory secretory phase (the luteal phase), and a menstrual phase. During the follicular phase the endometrial cells proliferate and the lining thickens under the influence of estrogen. During the secretory phase, increasing amounts of progesterone reverses the proliferative effects of estrogen and facilitates decidualization of the endometrial stromal cells (ESC). Decidualization involves significant morphologic and functional differentiation of ESC [2]. Subsequently, progesterone withdrawal in the absence of embryo implantation, leads to sloughing off of the upper functional layer of endometrial tissue (i.e., the decidua) and menstrual bleeding. The endometrium then regenerates from the basal layer.

In the beginning of the menstrual cycle, the endometrium appears ultrasonographically as an echogenic line of about 1-4 mm in thickness. This increases during the proliferative phase, measuring up to 11mm just before ovulation. During the progesterone-mediated secretory phase, the endometrial lining thickens further, with measurements ranging from 7-16mm [3].

The first step in progesterone synthesis, as in all steroidogenesis, is the conversion of cholesterol to pregnenolone, which is then metabolized to progesterone via the 3β-hydroxysteroid dehydrogenase enzyme. These processes occur both in ovarian follicular cells and the adrenal cortex. Adrenal progesterone does not play a significant role in the presence of normal mature ovaries, which produce a substantial amount of progesterone during the luteal phase. Adrenal progesterone may only have a potential role in the setting of ovarian failure, particularly in conjugation with exogenous estrogen exposure. For example, ovariectomized rats have been found to have decreased adrenocortical activity. After estradiol injection, these rats were noted to have a prominent capsule, expanded zona glomerulosa cells, and increased vascularization in the adrenal medulla [4]. Lobo et al., found that administration of conjugated estrogens in oophorectomized women (n=10) resulted in increased adrenal androgens and cortisol [5]. However, De Geyter et al had contrasting results, finding that ACTH-stimulated increase in progesterone levels was significantly blunted in the presence of ethinyl estradiol [6]. Our patient was not on conjugated estrogen or ethinyl estradiol therapy, but was on transdermal estradiol; the possible effects of this on adrenocortical function remains to be determined.

There is some evidence suggestive of the possible contribution of adrenal progesterone in the menstrual cycle. LH receptors are present in the adrenal cortex [1], and adrenal progesterone production has been postulated to play a role in progesterone increase during the follicular phase [6,7]. De Geyter et al., found that in patients with initially elevated progesterone levels during the follicular phase, dexamethasone suppression of the adrenal cortex resulted in subsequently lower progesterone levels. In this study, a subpopulation of 20 women with normal ovulatory function were given GnRH agonists. Those with subsequent progesterone levels of >0.6 ng/mL were randomized to receive dexamethasone suppression (n=12) vs. not (n=8). Upon ovarian stimulation, those who received dexamethasone had significantly lower progesterone levels (1.09 +/- 0.18) compared to those who did not (2.32 +/- 0.47) [6]. This suggests a crosstalk between the ovaries and adrenal glands, and that adrenal production of progesterone may contribute to progesterone increase at least during the follicular phase. Similar conclusions were drawn from a similar study by Eldar-Geva et al. [7]. Furthermore, Alevizaki et al., found that chronically elevated LH levels in post-menopausal women was positively correlated with cortisol and DHEA-S levels, suggesting that elevated LH levels may stimulate adrenal function. Interestingly, this effect was significant only up to an LH level of 41 U/L, suggesting possible saturation of adrenocortical LH receptors [8]. Progesterone levels in this study were not measured.

Physiologically, estrogen is known to increase progesterone receptor expression in the endometrium during the secretory phase [2]. Exogenous estrogen exposure could thus potentially enhance endometrial progesterone sensitivity. Although there is a lack of data, we propose that the transdermal estradiol in our patient could have allowed her adrenally produced progesterone to cause a partial secretory phase leading to regular bleeding episodes. Our study is limited in that we were unable to examine the endometrial tissue in more detail. There is also a lack of normative data on progesterone levels in adolescents with ovarian failure.

In this report, estrogen replacement therapy was initiated for primary ovarian failure, and regular menstrual bleeding was observed without exogenous progesterone replacement for 16 months. This led us to search for the non-ovarian source of progesterone, which would be adrenal. The supportive evidence, albeit weak and indirect, did substantiate the potential role of adrenal progesterone in the maturation of estrogen-primed endometrial lining leading to menses at fairly regular intervals. However, it still remains elusive to determine the cyclicity of adrenal progesterone, causing regular menses. As we continued carefully following up our patient, we did notice the thicker endometrial lining by ultrasound, even on days 2-4 post-LMP. This raised a concern over insufficient shedding of the endometrial lining, perhaps either due to insufficient endogenous source of adrenal progesterone or continued effects of TDE on endometrial proliferation. This could lead to the risk

of endometrial hyperplasia in the long term. Thus, exogenous progesterone challenge for 7 days was recommended and has been planned for every 3 months.

Conclusion

Although extremely rare, patients with Turner Syndrome and primary ovarian failure may develop regular menses on estrogen therapy without progesterone replacement, at least in the short term. Adrenal progesterone in these patients may partially assist in the maturation of the endometrial lining and regulation of menses.

References

1. Pabon JE, Li X, Lei ZM, Sanfilippo JS, Yussman MA, Rao CV. Novel presence of luteinizing hormone/chorionic gonadotropin receptors in human adrenal glands. J Clin Endocrinol Metab. 1996. 81: 2397-2400.
2. Okada H, Suzuki T, Murata H. Decidualization of the human endometrium. Reprod Med Biol. 2018; 17: 220-227.
3. Nalaboff KM, Pellerito JS, Ben-Levi E. Imaging the endometrium: disease and normal variants. Radiographics. 2001; 21: 1409-1424.
4. Saruhan BG, Ozdemir N. Effect of ovariectomy and of estrogen treatment on the adrenal gland and body weight in rats. Saudi Med J. 2005; 26: 1705-1709.
5. Lobo RA, Goebelsmann U, Brenner PF, Mishell DR Jr. The effects of estrogen on adrenal androgens in oophorectomized women. Am J Obstet Gynecol. 1982. 142: 471-478.
6. De Geyter C, De Geyter M, Huber PR, Nieschlag E, Holzgreve W. Progesterone serum levels during the follicular phase of the menstrual cycle originate from the crosstalk between the ovaries and the adrenal cortex. Hum Reprod, 2002. 17: 933-939.
7. Eldar-Geva T, Margalioth EJ, Brooks B, Algur N, Zylber-Haran E, Diamant YZ. The origin of serum progesterone during the follicular phase of menotropin-stimulated cycles. Hum Reprod. 1998; 13: 9-14.
8. Alevizaki M1, Saltiki K, Mantzou E, Anastasiou E, Huhtaniemi I. The adrenal gland may be a target of LH action in postmenopausal women. Eur J Endocrinol. 2006; 154: 875-881.