Evaluation Of Secondary Amenorrhoea By Vaginosonographic Measurement Of Endometrial Thickness.

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Summary

A progesterone challenge test is the routine method to evaluate endogenous estrogen status in secondary amenorrhoea. A favourable response to this test depends upon the priming of the endometrium by the endogenous estrogen.

Transvaginal ultrasonography was done to measure the endometrial thickness and to determine the sensitivity of this method in predicting the response to progesterone challenge test in 35 women with secondary amenorrhoea. Endometrial thickness of women who withdrew to progesterone challenge was 0.73 ± 2.1 cms and a significantly thinner endometrium of 0.25 ± 0.2 cms was observed in cases, who did not withdraw.

Urinary estrone glucuronide values were significantly ($p < 0.05$) higher in women who withdrew with progesterone challenge.

The sensitivity of this method of evaluation in predicting a response to progesterone challenge was 90% and the specificity was 100%.

Hence, transvaginal ultrasonographic measurement of the endometrial thickness in women with secondary amenorrhoea is a good method for evaluating the response to a progesterone challenge test.

Introduction

Secondary amenorrhoea is a stressful condition and accounts for nearly 20-30% of consultations in a gynaecological endocrine clinic. In a referral infertility clinic, 30-35% of women seek consultation for irregular cycles and infertility.

Laboratory estimation of endogenous estrogen status is an expensive test. Diagnosis of the various causes of secondary amenorrhoea requires estimation of serum FSH, LH, PRL and testosterone.

A normal level of serum gonadotropin (S. Gntr) and serum estradiol suggests hypothalamic dysfunction while an elevated S. Gntr. levels with low level of endogenous estradiol suggest ovarian failure. The latter groups will not respond to ovulation inducing agents while the former is known to respond to drugs required for ovulation.

There is a wide variation of estradiol values observed in serum levels. The effect on the priming of endometrium by endogenous estrogen does not vary (Shulman et al, 1989). Hence, as an alternative progesterone challenge test has been used as a bioassay to determine the endogenous status. In order to predict a patient's response to ovulation induction by antiestrogens adequate levels of endogenous estrogen is essential. The basis for this test is that an estrogen primed endometrium will respond to progesterone administration by a good withdrawal bleeding noticed 5-10 days after oral or intramuscular administration of progesterone. Women with low or poor endogenous estrogen will either have very scanty or no withdrawal bleeding.

Progesterone challenge test has few drawbacks by way of delay in observation of the response of withdrawal bleeding and a repeat clinic visit. Vaginal ultrasonography has opened new vistas in the evaluation of pelvic organs and detecting ovarian disorders such as cysts, polycystic ovaries and cystic ovaries which were earlier diagnosed only at a laparoscopic examination. The method is simple, quick and less cumbersome as it does not require full bladder examination. It provides good visualization of the endometrium and ovaries and is now widely used. We therefore, undertook a study with the following objectives.

Aims and Objective

a) Vaginosonographic measurement of the

endometrial thickness to predict the response to progesterone test.

b) Sensitivity of this method of evaluation of secondary amenorrhoea as compared to progesterone test.

Subjects and Method

Thirty-five women with the age range of 19 to 30 years having secondary amenorrhoea (absence of menses for more than 3 months duration) were enrolled at the Infertility Clinic of the Institute for Research in Reproduction, Mumbai. After ascertaining that no drugs for withdrawal bleeding or for irregular cycles were taken within 6 weeks, blood sample (5 ml) was drawn for estimation of prolactin and testosterone by RIA method. Early morning urine samples were collected for estimation of follicular stimulating hormone (FSH), luteinizing hormone (LH) and estrone glucuronide (E_1G) by ELISA on the day of ultrasonography examination. Estimation of T_3, T_4 and TSH for thyroid evaluation were also done.

After careful history and clinical examination, vaginal sonography for measurement of endometrial thickness was performed on an empty bladder by a single observer with a Philips 5 MHz vaginal probe by a method described by Morcos et al., (1991). The uterus was visualized in the saggital plane. The caliper was placed anteriorly at the interphase between the endometrium and myometrium at the maximum area of thickness i.e. the fundus of the uterus. Similarly, the second caliper marking was at the interphase between endometrium and myometrium on the posterior wall of the uterus (Fig. 1) .

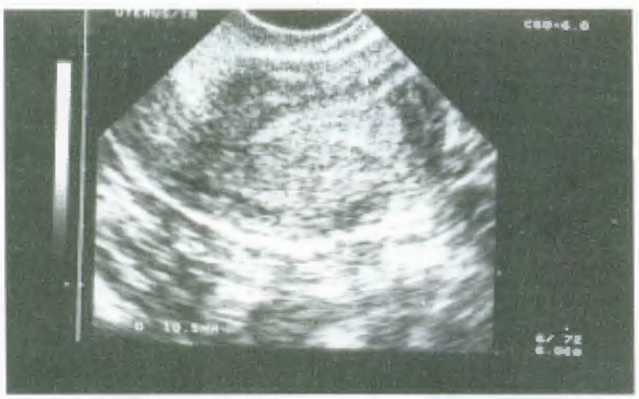

Fig. 1 Measurement of endometrial thickness

The endometrial thickness was noted. The ovarian and uterine morphology viz. ovarian cyst, polycystic ovary and presence of uterine fibroid if any, were observed. The patient was then asked to take an oral progesterone preparation (medroxy-progesterone acetate10 mg one daily for 5 days) and to report withdrawal bleeding. The duration and number of days of bleeding were recorded. The test was considered positive if the woman withdrew with a good menstrual flow of 2-3 days. Negative progesterone challenge test was either spotting or no menstrual bleeding.

Results

Of the 35 amenorrheic women, who were given a progesterone challenge test (Tab. Medroxy Progesterone acetate- 10 mg daily for 5 days), 18 had withdrawal bleeding and 15 did not withdraw while 2 had spotting only.

The average weight of the women in both the groups did not vary. The 18 cases which had withdrawal bleeding had an average of 12 weeks, of amenorrhoea whilst, the 17 cases who had negative withdrawal bleeding had on an average 20 weeks, of amenorrhoea (Table I).

Table I : Progesterone Challenge Trust

	Withdrawal (N=18)	No withdrawal (N=17)
Age	24.72 ± 5.30	28.82 ± 6.36
Weight in Kgs.	49.94 ± 14.78	48.05 ± 10.04
Amenorrhoea in weeks	12.88 ± 3.30	20.82 ± 5.70

In all the cases besides the routine investigations for amennorrhoea (viz.FSH, LH tfhyroid and prolactin estimation) the estrone glucuronide (E_1G) level in urine was estimated Urinary E_1G level in women, who withdrew to progesterone challenge was 23.01 ± 7.3 ng/mgC and women, who did not withdrew (spotting/ no bleeding to progesterone challenge) had lower E_1G values o 18.28± 6.03 ng/mgC, the difference statistically significant ($p<0.5$) (Table II).

Table II: Endogenous Estrogen status and Endometrial thickness in Amenorrheic women: Response to Progesterone Challenge

	Withdrawal (N=18)	No Withdrawal (N=17)
E_1G ng/mgC	23.01 ± 7.33	18.28 ± 6.03 ($p < 0.05$)
Endometrial thickness (cms)	0.73 ± 0.21	< 0.25 ± 0.27 ($p < 0.001$)

The mean endometrial thickness was 0.73cm, range being 0.4 cm to 1.1 cm, in the withdrawal group and 0.25cm or less in the no withdrawal group. This difference was also statistically significant ($p<0.001$). The sensitivity of this method of evaluation of secondary amenorrhoea was 90% and specificity 100%.

Seven cases of polycystic ovarian disease (PCOD) and 11 cases of hypothalamic pituitary dysfuction (HPD) had withdrawal bleeding, better estrogen status (E_1 G- 23.0 ± 7.33 ng/mgC) and thicker endometrium (0.73 cms) PCOD was diagnosed clinically and by ultrasonography with altered FSH/ LH ratio. However, testosterone and prolactin values were within normal range in these women. Women with hypothalamic pituitary dysfunction (HPD) showed gonadotropin, testosterone and prolactin values in the normal range.

Eight women with premature ovarian failure (POF) had increased FSH (normal range 6-48 mIU/ ngC). Two cases had gonadotropin resistant syndrome (GRS) (increase gonadotropins with ovary showing few follicles on ultrasonography). Five cases of end organ failure and 2 cases of hypothalamic pituitary failure (low FSH, LH values) had negative withdrawal bleeding, low estrogen status (18.28± 6.03 ng/ mgC) and poor endometrial thickness of $\leq$ 0.2cms Table III).

Table III: Provisional Diagnosis of Secondary Amenorrhoea

	Withdrawal (N=18)	No Withdrawal (N=17)
Provisional diagnosis	1) PCOD — 7 2) HPD — 11	POF -8 Gonadotropin Resistance Syndrome -2 Endorgan Failure -5 Hypothalamic Pituitary Failure -2

Discussion

The women in this study were those who came for the treatment of amenorrhoea and infertility. Progesterone challenge test is given as a traditional method for evaluation of amenorrhoea. Women who respond to progesterone test by a withdrawal bleed have a better response to ovulation induction by clomiphene citrate or human menopausal gonadotropin. The ones who do not respond have a poorer reproductive outcome.

In our study, the endometrial thickness of less or equal to 0.2 cms could predict a negative progesterone challenge test in 15 out of 17 cases. The sensitivity was 90% and specificity of the method was 100%. Morcos et al., (1991) observed a negative progesterone challenge test in women whose endometrial thickness was < 1.5 cms. Shulman et al. (1989) observed that endometrial thickness < 0.4 cms did not have a withdrawal bleeding to progesterone challenge and there was correlation coefficient of 71% ($p = 0.001$) between endometrial thickness and E_2 levels. Serum estradiol or total estrogen levels may fluctuate (Hull et al., 1979). Therefore, single serum estimation does not give the correct picture of the endogenous estrogen effect on the endometrial thickness.

The measurement of endometrial thickness by transvaginal sonography gives a total endogenous estrogenic effect on the endometrial thickness over the period of amenorrhoea. This technique is safe and acceptable to the patients as compared to the full bladder techniques and the procedure gives a good visualization of the ovaries, the uterus and adenexae for better diagnosis enabling a provisional diagnosis to be made at the first visit.

In conclusion, this method of transvaginal ultrasonography for endometrial thickness evaluation of secondary amenorrhoea is less time consuming and less cumbersome and has a high sensitivity and specificity for predicting a negative or positive progesterone test.

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