Changes in the Hormonal Profile of Ovariectomized Women in the Course of Fetal Therapy

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Changes in the hormonal profile after human fetal tissue transplantation are studied in ovariectomized women of reproductive age. Normalization of the hormonal profile is achieved for at least 5-6 months after the first procedure and for at least 9-10 months after repeated inoculation of fetal tissue.

Key Words: *postovariectomy syndrome; hormonal profile; human fetal tissue transplantation*

Hormonal disorders associated with the postovariectomy syndrome primarily involve changes in the secretion of luteinizing (LH) and follicle-stimulating (FSH) hormones, progressing because inhibin is not produced by the ovaries and the negative feedback between estrogens and the hypothalamo-hypophyseal area is impaired.

Increased levels of FSH and LH after oophorectomy are believed to be associated with hyperfunction of the anterior lobe of the hypophysis [1,2]. Recently, special attention has been focused on the role of opioid peptides in the pathogenesis of the postovariectomy syndrome. Opioid peptides were found to contribute to the regulation of the hypothalamo-hypophyseal hormonal secretion [3]. Analysis of the effects of opioid peptides on the hypothalamo-hypophyseal-gonadal system is important for the correction of postcastration disorders.

Synthetic and natural estrogens and gestagens do not provide adequate correction of the postovariectomy syndrome and induce a number of side effects. Replacement hormone therapy is contraindicated in patients with liver and kidney diseases, varicous veins (transitory hypercoagulation is developed), and thrombophlebitis. Breast and endometrial cancer have been reported; a regular menstrual-like reaction caused discomfort in females with preserved uterus.

Human fetal tissue transplantation (HFTT), which has no side effects on the recipient's organs and tissues, is a prospective method for the prevention and therapy of the postovariectomy syndrome.

MATERIALS AND METHODS

In order to assess integral restructuring of the neuroendocrine system hormonal profiles were studied in 53 women of reproductive age (33.3±2.1 years) after total ovariectomy.

The women were operated for benign tumors and neoplasms of the ovaries and benign tumors of the uterus (disease duration 0-3 years).

Gonadotropic hormones (LH and FSH), estradiol, progesterone, prolactin, testosterone, cortisol, and thyrotropic hormone were measured by enzyme immunoassay in an Amerlite analyzer. Highly specific antisera not cross-reacting with other naturally occurring substances were used. The results were compared with the reference values for the studied hormones, which were calculated using the parameters measured in healthy women during the early follicular phase of menstrual cycle.

Fetal tissue for HFTT was obtained from 15-40-year-old women. The gestation age of fetuses weighing 200-450 g varied from 16 to 20 weeks.

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RESULTS

The mean levels of LH and FSH in women with the postovariectomy syndrome were 38.5 and 58.1 U/liter, respectively, which is 8 and 17 times higher than in healthy age-matching controls. Monthly measurements after the first HFTT showed a significant drop of LH and FSH levels. The maximum decrease in the serum FSH content was observed during the second month (15.1 U/liter) and in the LH content by the third month (12.3 U/liter, after which it gradually increased until the eleventh month, approaching but not attaining the initial level (Fig. 1, *b*).

The decline of the effect in 15 out of 53 patients prompted us to repeat HFTT on the eighth month of the observation period. The FSH level dropped almost 4-fold as early as after the first month (14.3 U/liter) in comparison with the initial value, and decreased until the sixth month (11.8 U/liter). A tendency towards a continuous increase in the FSH concentration was observed, but even by the eleventh month it was more than 2.5-fold lower than the initial value (22.2 U/liter, Fig. 1, *a*).

Luteinizing hormone was more sensitive to repeated HFTT. Its minimal serum content was recorded 8 months after a second HFTT (9.4 U/liter). This corresponded to the reference values for the first phase of the cycle (Fig. 1, *b*).

In healthy young women, the concentrations of estradiol and progesterone are 86-677 pmol/liter and

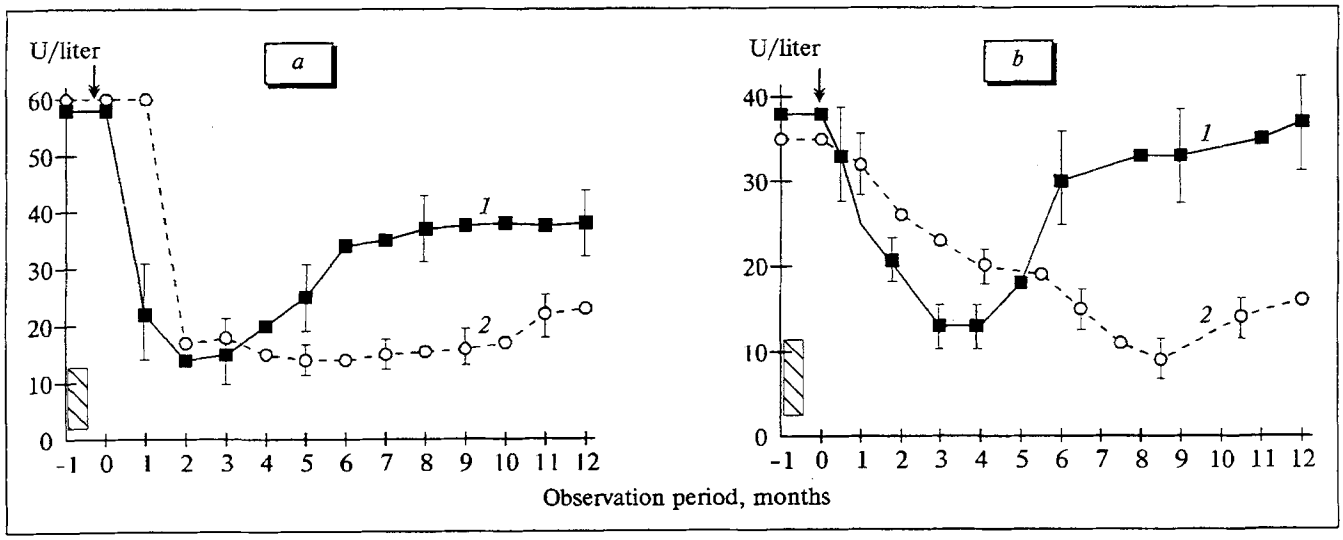

Fig. 1. Plasma contents of follicle-stimulating (*a*) and luteinizing (*b*) hormones in ovariectomized women after the first (*1*) and second (*2*) transplantation of human fetal tissues. Here and on Figs. 2 and 3: the shaded area represents normal values, the arrow shows the time of transplantation.

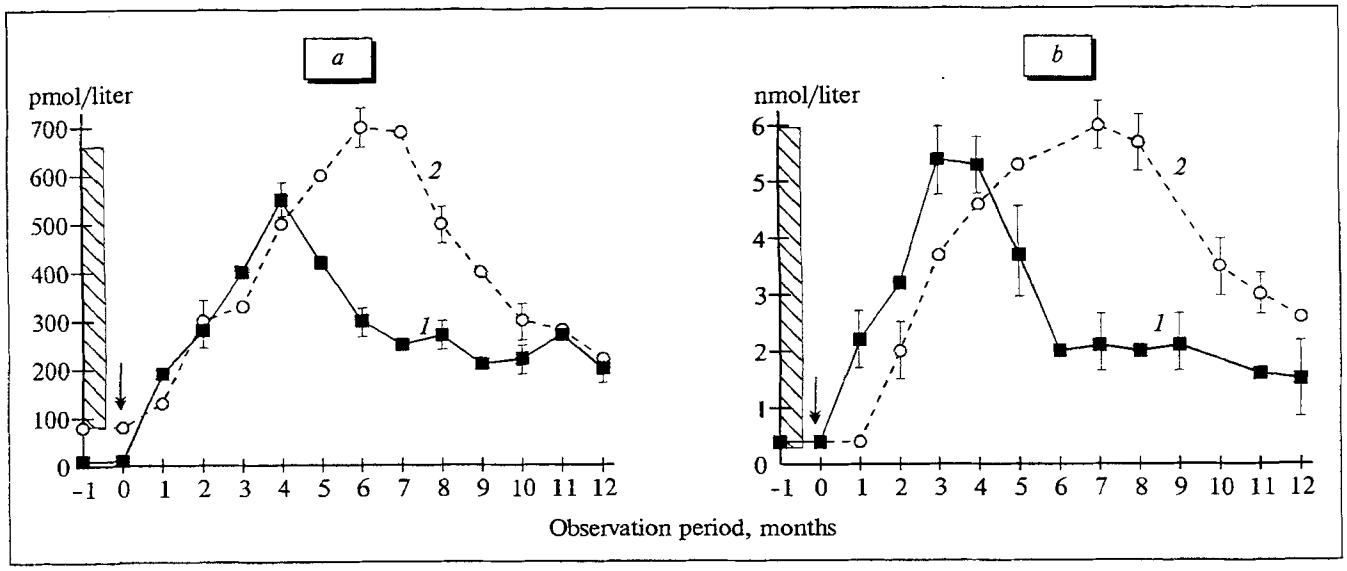

Fig. 2. Plasma contents of estradiol (*a*) and progesterone (*b*) in ovariectomized women after the first (*1*) and second (*2*) transplantation of human fetal tissues.

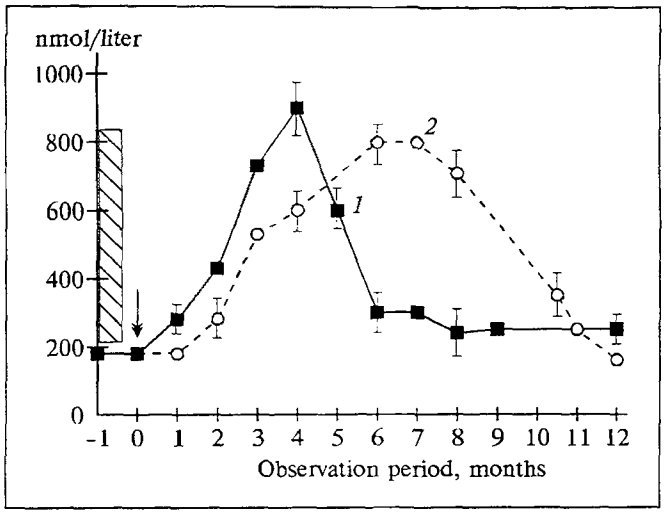

Fig. 3. Content of cortisol in the blood plasma in ovariectomized women after the first (*1*) and second (*2*) transplantation of human fetal tissues.

0.1-4.3 nmol/liter, respectively. Ovariectomy in reproductive age causes a drop in the levels of these hormones to 10 pmol/liter and 0.42 nmol/liter, respectively, in comparison with those in healthy women.

Even the first HFTT provided a significant increase in the estradiol and progesterone contents, which were normalized by the 3rd month and gradually decreased starting from the fifth month. Repeated HFTT had a more pronounced and prolonged positive effect than the first one, normalizing the levels of these hormones (Fig. 2, *a*, *b*).

After ovariectomy, the prolactin level remained virtually the same as in healthy subjects. Neither the first nor the second HFTT induced any significant changes in the prolactin content, implying that the therapy had no effect on it.

The testosterone content after the surgery corresponded to the lower threshold value in health (1.4 to 1.9 mmol/liter). After the first HFTT, it increased by the 3rd-4th month of the observation period, and gradually decreased to the initial value. The same tendency was observed after repeated HFTT, the only difference being that its maximum serum content dropped during the 5th-7th months. Interestingly, the testosterone concentration during the therapy varied within the normal range. The relatively low concentration of this hormone after ovariectomy may result from the cessation of its production in the ovaries. Presumably, HFTT stimulates its formation in the adrenals.

The same tendency was observed with the cortisol blood level: during the treatment it varied within the normal range (Fig. 3). The hypophyseal-thyroid status was assessed from the serum concentration of thyrotropic hormone. Both HFTT lowered the hormone concentration in the serum throughout the observation period.

Thus, HFTT increased the estradiol and progesterone levels, which probably facilitates the decrease in the serum concentrations of gonadotropic hormones. The level of prolactin remained virtually the same during the observation period.

Although the initial levels of cortisol and testosterone were relatively low (but not lower than the normal threshold value), they gradually increased to relatively high values (but not higher than the upper threshold value) (Fig. 3).

Changes in the cortisol and testosterone levels may account for the complications and disappearance of vegetative and psychoemotional complexes of symptoms and for a lower annual loss of minerals from bones, i.e., the progression of postcastration osteoporosis, which confirms the antiresorptive effect of HFTT. Therefore, HFTT may become an alternative method for the treatment of women with the postovariectomy syndrome.

REFERENCES

1. V. P. Smetnik and A. A. Kangel'dieva, *Akush. Gin.*, No. 8, 5-9 (1988).
2. G. Berg and M. Hammar, *Acta Obstet. Gynecol. Scand. Suppl.*, **132**, 9-12 (1985).
3. W. Hermens, Z. Belder, and J. Merkus, *Eur. J. Obstet. Gynecol. Reprod. Biol.*, **40**, No. 1, 35-41 (1991).