

Examination of the breasts 6-8 months after THFT revealed no deterioration: the glandular matrix structure was intact and there were no signs of nodular proliferates.

Thorough clinical examinations and patient interviews showed that along with improved wellbeing, decrease of feverishness, sweating, and irritability, and increased work capacity, an improvement of skin turgor was observed, including that of the breasts. The breast became more elastic and plastic, even though mammography did not detect any increase in the volume of glandular structures.

The preliminary results of the use of THFT in the treatment of patients with the postcastration syndrome permit us to regard with optimism the potentials of this method to correct the serious aftereffects of bilateral oophorectomy.

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Experimental Treatment of Habitual Abortion of Adrenal Etiology by Transplantation of a Tissue Culture of Newborn Pig Adrenals

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Transplantation of an adrenal tissue culture from newborn pigs was performed in patients with habitual abortions. The advantages of this method as compared to the traditional treatment with adrenocortical hormones consist in the absence of effects on the fetus and of side effects in pregnant women. Monitoring of the serum level of adrenocortical hormones is not required. Healthy children were born to 22 patients out of 23. Three clinical cases are described.

Key Words: *transplantation of fetal tissues; treatment of habitual abortion; adrenal hypofunction*

Habitual abortion due to impaired adrenal function is frequent among cases with a late diagnosis (26.6%) [1] as well as with an early diagnosis and

when treatment is begun prior to conception (15-20%) [3].

The most common adrenal diseases, causing habitual abortion are congenital dysfunction of the adrenal cortex, namely its mitigated forms with 21-hydroxylase or 11-hydroxylase deficiency, and

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primary adrenal insufficiency (Addison's disease) of various etiology (autoimmune, infectious, postoperative, mycotic, etc.).

Replacement therapy with glucocorticoids and mineralocorticoids [4] is widely used as treatment for infertility aimed at the correction of cortisol deficiency and of the levels of mineralocorticoids and androgens. However this method has significant disadvantages:

1. The use of synthetic analogs of cortisol in the first trimester leads to known anatomic defects in the fetus (cleft lip and palate), while long-term therapy with high doses causes atrophy of the adrenal cortex and inhibited growth of the fetus [3].

2. The frequency of side effects with the chronic use of glucocorticoids is nearly 50% [5].

3. The laboratory methods available to clinicians (levels of cortisol, 17-ketosteroids, and ACTH) reflect the steroid level of the patient which is inhibited by the administration of synthetic glucocorticoids, and so do not make it possible to select the therapeutic doses flexibly and accurately or to minimize the negative consequences of replacement therapy.

The aim of the present investigation was to study the possibilities of preserving pregnancy, of compensating for the cortisol deficiency, and of lessening the consequences of the traditional method of treatment by transplanting an adrenal tissue culture from newborn pigs.

MATERIALS AND METHODS

The patients represent a heterogeneous sample in terms of age and number of abortions, collected from 1988 to the present at the Department of Pregnancy Pathology of the Research Institute of Obstetrics and Pediatrics. The following criteria were used to select patients: 1. A history of habitual abortion. 2. Clinical features of hypocorticism or hypocortisolism and hyperandrogenism in the present pregnancy. 3. Symptoms of threatened abortion.

The group under study consisted of 23 patients aged from 22 to 38 years. They had a history of 1 to 9 abortions or premature births, symptoms of hypocorticism (Addison's disease) (12 women) or hypocorticism with hyperandrogenism (congenital dysfunction of the adrenal cortex) (11 women), and all of them were under threat of abortion at the time of the investigation. The patients were grouped together since they could all be classified under a common syndrome of "hypocortisolism" as a result of a drop and/or impairment of cortisol synthesis and secretion.

The transplantation of the adrenal tissue culture was performed at various stages of pregnancy from 5 to 31 weeks.

Preparation of the adrenal tissue culture was performed by the method approved for clinical use at the Kiev Research Institute of Endocrinology and Metabolism [6]. After 5-7 days of culturing the adrenal tissue culture was deemed suitable for transplantation. The tissue culture was separated from the nutrient medium, washed with saline, transferred to sterile flasks, and delivered to the clinic.

The tissue was transplanted under the aponeurosis of m. rectus abdominis, 3-4 cm above the umbilicus at the level of the linea medioclavicularis. The tissue culture was administered under local novocain anesthesia through a thick injection needle under aseptic conditions. The dosage was 200-300 mg/10 kg of body weight depending upon the clinical and laboratory findings of the degree of hypocortisolism in each case.

The efficacy of the transplantation was assessed by the change of cortisol and ACTH levels, disappearance of hypocorticism or hypocortisolism and hyperandrogenism, and by the final result, namely the maintenance of pregnancy and normal labor with a healthy infant.

RESULTS

Full-term delivery of a healthy infant occurred in 22 of the 23 patients; one patient had a spontaneous abortion after 16 weeks of pregnancy.

The study of cortisol in the late stages of pregnancy showed a complete compensation of adrenal function in all the women, the cortisol level being 440-1600 nmol/liter. The incidence of abortion in the studied group was 4.4%.

The frequency of complications due to the glucocorticoid therapy was practically zero since there was no need for prolonged replacement therapy.

The average weight of the newborn infants was 3100 g.

The following clinical cases are of interest.

First case. Patient Ya-ko, case record № 464/2367, 22 years old, height 170 cm, weight 49 kg. The admitting clinical diagnosis: pregnancy of 11 weeks, threatened spontaneous abortion, early gestosis, a history of one spontaneous abortion. The clinical and laboratory workups revealed Addison's disease of moderate degree. The blood cortisol level was 64.2 nmol/liter (norm 230-750 nmol/liter), the content of 17-ketosteroids in the urine was 1.5 mg/day (norm 7.5-17.5 mg/day).

The patient was treated by transplantation of a pig adrenal tissue culture in a dose of 300 mg per 10 kg body weight at 12 weeks. Seven days later the condition of threatened abortion no longer existed. The patient was discharged from the hospital in satisfactory condition.

The follow-up examination showed the absence of threatened abortion and full compensation of adrenal function. The blood cortisol level was 640.6 nmol/liter 2 months after the transplantation, and 890 nmol/liter 3 months after the transplantation. The content of 17-ketosteroids in the urine was 9.2 mg/day on the 13th day after the transplantation.

The patient did not need glucocorticoid therapy during the whole pregnancy. A normal labor and healthy infant were the outcome of this pregnancy.

Second case. Patient Zh-ova, case record № 181/1000, 28 years old, height 162 cm, weight 91 kg. Clinical diagnosis on admission: pregnancy of 6 weeks, threatened abortion. The anamnesis noted one spontaneous abortion at 10-11 weeks in 1978, a second spontaneous abortion in 1979, a third one at 8-9 weeks in 1984, and a fourth one at 6 weeks in 1986. In 1987 surgery was performed for the syndrome of polycystic ovaries, and after that a fifth spontaneous abortion at 6 weeks occurred in 1988 and a sixth one at 24 weeks in 1989.

The clinical and laboratory investigation revealed congenital dysfunction of the adrenal cortex (mitigated form). Hypocortisolism of the first degree. Hyperandrogenism. Hirsutism. Pregnancy of 6 weeks. Threatened spontaneous abortion. The blood cortisol level was 200 nmol/liter (norm 230-750 nmol/liter), the level of ACTH was 70 ng/liter (norm 0-50 ng/liter), the content of 17-ketosteroids in the urine was 22.0 mg/day (norm 7.5-17.5 mg/day).

Transplantation of a pig adrenal tissue culture in a dose of 200 mg per 10 kg body weight was performed at 8 weeks. Fourteen days later the condition of threatened abortion was absent.

The clinical follow-up examination confirmed compensation of adrenal function. The blood cortisol level was 360 nmol/liter on the 5th day after the transplantation and 440 nmol/liter 3 months later; the level of ACTH was 1.0 ng/liter 3 months after the transplantation, and the content of 17-ketosteroids in the urine was 13.0 mg/day 1 month after transplantation.

The clinical follow-up confirmed the compensation of hypocortisolism and hyperandro-

geny. Pregnancy ended in normal labor and a healthy child.

Third case. Patient E-va, case record № 1124/7071, 37 years old, height 154 cm, weight 65 kg. Clinical diagnosis: pregnancy of 29 weeks, threatened spontaneous abortion. Primary chronic III degree adrenal insufficiency, postoperative decompensation (both adrenals were removed in 1956 due to Cushing's disease). The patient has a history of one abortion and one normal labor with a healthy child. She has been receiving continuous therapy with prednisolone, 10 mg/day.

The admitting blood cortisol level was 160 nmol/liter and the level of ACTH was 180 ng/liter. Transplantation of an adrenal tissue culture in a dose of 300 mg per 10 kg body weight was performed at 31 weeks of pregnancy. Ten days later the condition of threatened abortion was abolished. The laboratory workup confirmed compensation of adrenal function. The blood cortisol level was 440 nmol/liter on the 2nd day after the transplantation and 600 nmol/liter 1 month later; the content of 17-ketosteroids in the urine was 10 mg/day 2 days later and 8.8 mg/day 20 months after transplantation. A normal labor and delivery took place.

Based on the findings, two conclusions may be drawn: 1) the method of transplantation of a tissue culture of the adrenal cortex makes it possible to compensate for an endogenous deficiency of cortisol and to minimize glucocorticoid therapy in pregnant women; 2) it is advisable to determine organospecific immunoglobulins (stimulating steroidogenesis and mitogenesis in adrenal cortex cells) in the serum of treated patients.

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