Two routes of hormonal replacement therapy in symptomatic menopausal women after kidney transplantation

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Submitted: March 30, 2006 *Accepted: May 12, 2006*

Key words: **kidney transplantation; climacteric symptoms; hormonal replacement therapy; menopause; immunosuppression**

Neuroendocrinol Lett 2006; **27**(3):387–391 **PMID:** 16816826 NEL270306A17

Abstract

OBJECTIVES: The assessment of efficacy and safety of two regimens of hormonal replacement therapy (HRT) in women after kidney transplantation with climacteric symptoms.

MATERIAL AND METHODS: Combined transdermal or transdermal-oral hormonal replacement therapy was administered to 86 kidney-transplanted women, aged 31-52 years, with moderate to severe climacteric symptoms in years 1995–2005. The patients underwent follow-up examinations one, three and six months after onset of the therapy and every four months subsequently. Blood pressure, body weight, sex hormone profile, serum parameters of both kidney and liver function, endometrial image in transvaginal sonography and reduction of climacteric symptoms were assessed.

RESULTS: The mean time of the therapy was 5.6 years for transdermal-oral regimen (54 patients) and 4.7 years for transdermal regimen (32 patients). Most patients reported reduction of climacteric symptoms and improved life quality after 6 months of HRT. 28% of women discontinued therapy for medical indications, most often due to significant deterioration of liver function. One case of profound vein thrombosis was noted. 21% of women decided to discontinue therapy after the results of the WHI trial had been published.

CONCLUSIONS: Hormonal replacement therapy is effective in climacteric symptoms relief and improvement of life quality in kidney transplanted women. Higher rate of side effects observed in that group of patients contributes to the need for frequent, attentive surveillance. Further studies should be conducted to establish the optimal doses and routes of administration of HRT as well as to assess the range of necessary follow-up examinations.

ORIGINAL ARTICLE

Abbreviations & units:

E_2	– estradiol
FSH	– follicle stimulating hormone
WHI	– Women's Health Initiative
HERS	– Heart and Estrogen/Progestin Replacement Study
ASPAT	– aspartate aminotransferase
ALAT	– alanine aminotransferase
PAP smear	– Pappanicolau smear
TVS	– transvaginal sonography
SD	– standard deviation
l	– liter
dl	– deciliter
ml	– milliliter
pg	– picogram
mg	– milligram
IU	– International Units
mm	– millimeter

Introduction

Kidney transplantation is commonly accepted treatment of end-stage renal failure. The development of new operative techniques and new, more effective immunosuppressive agents has resulted in constantly increasing number of kidney-transplanted patients worldwide. Introduction of cyclosporine into the immunosuppressive treatment in seventies of the twentieth century followed by addition of new agents such as tacrolimus, mycophenolan mophetil and rapamycine into the immunosuppressive regimens led to the extension of graft survival period. Nowadays most graft-recipients are given the opportunity to lead normal life and continue their professional careers.

Until the end of 2004 there were 2771 female graft recipients with active graft in Poland. 818 women were between 45 and 55 years of age. Slow, but constant grow of the mean age at the time of grafting has been observed, only during the last decade from 38.3 years to 43.2 years [12]. Such tendency is associated with the increasing population of female graft recipient of menopausal age, who may benefit from the use of hormonal replacement therapy to achieve the best quality of life. Moreover hormonal replacement therapy seems to be particularly indicated in that group of women. Long period of uremia with the impaired function of the hypothalamus-pituitary-ovary axis results in chronic estrogen deficiency, and sometimes in premature menopause. There are also literature data revealing decreased levels of melatonin in hemodialyzed patients with end-stage renal disease [10]. Melatonin is well recognized as a hormone affecting both immunological and endocrine systems and its deficiency may influence different vital processes. Years of hemodialysis and long-term treatment with glicocorticosteroids increase the risk of osteoporosis development. Hormonal replacement therapy offers the patients relief of menopausal symptoms and urogenital atrophic changes as well as prevention and treatment of osteoporosis.

Until recently HRT was believed to decrease the risk and delay the development of cardiovascular diseases. In reflect of the results of the Heart and Estrogen/progestin Replacement Study – HERS [6] and the Women's Health Initiative – WHI [15] trial the HRT benefits on secondary prevention of cardiovascular diseases were challenged [7]. The role of HRT in primary prevention was also questioned. When final WHI reports and the results of the Million Women Study had been published, the recommendations for HRT use were created [3,14]. Experts expressed, however, their negative attitude to all mistakes associated with both of the trials and emphasized the opposite, beneficial aspects of HRT reported in observational studies [11,13].

There are few reports on HRT use in kidney transplanted women [1,9]. In the study we assess our ten-year-experiences in two regimens of HRT use (transdermal and transdermal-oral) in female kidney recipients.

Material And Methods

86 women after kidney transplantation, who received hormonal replacement therapy in years 1995–2005 were enrolled in the study. The mean age of patients on therapy onset ranged from 31 to 51 years (mean 44.5, SD 7.68). The period from transplantation varied from 3 months to 13 years (mean 5.8 years, SD 3.2). Before onset of the therapy the follicle stimulating hormone (FSH) levels were above 50 IU/l and estradiol (E_2) levels beneath 30 pg/ml in all graft recipients. All women reported moderate to severe menopausal symptoms assessed with the use of Kupperman index. Graft function was stable with serum creatinine levels varied from 0.7 to 1.9 mg/dl (mean 1.5 mg/dl, SD 0.23). All patients received individually adjusted regimens of immunosuppressive agents.

The underlying renal diseases were chronic glomerulonephritis (50 patients), chronic pyelonephritis (24 patients), policystic renal degeneration (4 patients) and renal failure of unknown origin (8 patients).

54 patients (group A) received transdermal-oral combined sequential HRT: 0.05 mg of estradiol daily for 21 days in transdermal path and 5 mg of lynestrenol orally for 12 days of the cycle. In seven-day-break in HRT administration uterine bleeding appeared. 32 patients (group B) with impaired initial parameters of liver function received transdermal combined continuous HRT: 0.05 mg of estradiol for 28 days and 250 mg of noretisterone acetate for 14 days of the cycle.

Examinations were performed on HRT onset, after one, three and six months of the therapy and every four months subsequently. Blood pressure, body weight and serum levels of creatinine, aspartate aminotransferase (ASPAT), alanine aminotranferase (ALAT), total bilirubin, FSH and estradiol were measured on every visit. The urogenital atrophy was assessed on gynecological examination. Data on the intensity of menopausal symptoms including hot flushes, night sweats, insomnia, nervousness, irritability, loss of concentration and depression were collected. PAP smear was obtained and mammography was performed on therapy onset and yearly afterwards in every patient. Furthermore every six months transvaginal sonography was performed with the special interest of endometrial thickness.

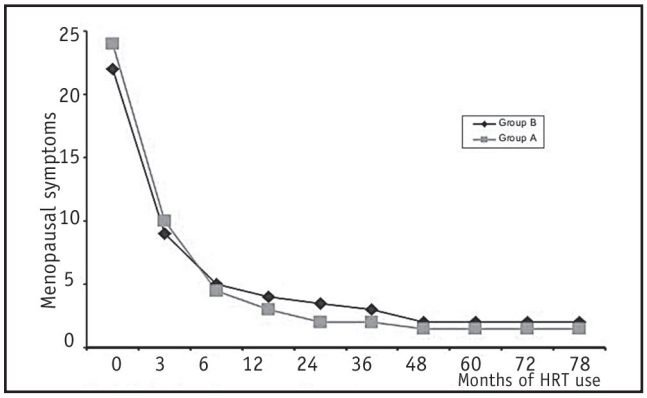

Fig. 1. Reduction of menopausal symptoms assessed with Kuperman index.

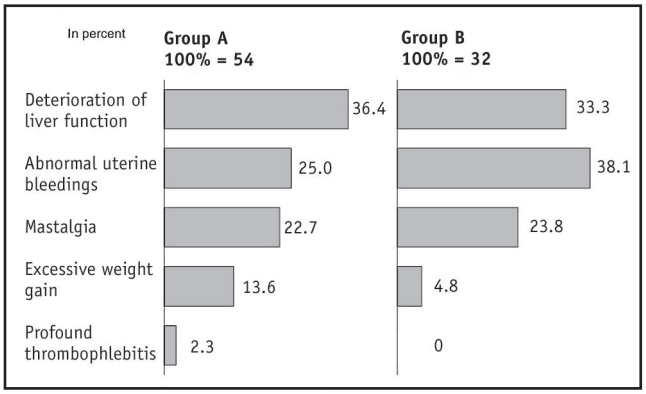

Fig. 2. Side-effectsof HRT observed in kidney transplanted women

Results

All patients from both groups reported beneficial effects as early as after the first course of HRT. After three months significant relief of climacteric symptoms was observed. After six months 80% of patients reported total regression of climacteric symptoms while the remaining group noted only mild complaints (Fig.1).

Significant decrease of FSH levels was observed after three months of the therapy: from 129 IU/l (SD 30.1) to 38 IU/l (SD 26.1) in group A and from 113 IU/l (SD 32.2) to 40 IU/l (SD 28.1) in group B. Simultaneously E_2 levels increased from 18.5 pg/ml (SD 5.8) to 98.6 pg/ml (SD 33.2) in group A and from 19.0 pg/ml (SD 9.5) to 88.9 pg/ml (SD 37.2) in group B.

All women experienced uterine bleedings of mild or moderate intensity after onset of HRT. 20% (11/54) of patients from group A and 25% (8/32) of patients from group B reported irregular staining or bleedings of mild intensity within the first year of the therapy.

The baseline endometrial thickness on TSV was 3.0 mm (1–5 mm) in group A and 3.5 mm (1–5 mm) in group B. After six months of HRT endometrial thickness assessed between 9th and 12th day of the cycle increased to 7 mm (4.5–12 mm) and 8 mm (5–13 mm) respectively. No case of endometrial cancer or hyperplasia was noted in the group of 19 graft recipients who underwent dilatation and curettage (D&C) for abnormal uterine bleedings or abnormal endometrial picture on TVS. Ten women from group A and five from group B experienced severe mastalgia during the first six months of the therapy. Spontaneous regression of complaints was observed in all patients. No case of breast cancer was noted in the study group. Serum creatinine levels remained stable. HRT did not lead to significant blood pressure increase. After six months of the therapy significant rise of body weight (over four kilograms) was noted in six patients from group A and in one patient from group B. Four of those women, however, received HRT in the first year after kidney transplantation and the observed weight gain may have been related rather to the post-transplant normalisation of metabolism than to the influence of HRT (Fig.2).

The mean time of the therapy was 5.6 years in group A and 4.7 years in group B. 24 patients discontinued therapy for medical indications. One woman from group A developed profound vein thrombosis and the remaining patients had significant deterioration of liver function (Fig. 3, 4, 5). 18 patients decided to discontinue therapy, in most cases after the results of the WHI trial had been published.

Discussion

Symptoms associated with estrogen deficiency lead to considerable deterioration of life quality in vast majority of menopausal patients. Menopausal female graft recipients additionally suffer from long-term consequences of the underlying disease and side effects of immunosuppressive therapy. Hormonal replacement therapy is known to be the most effective method of climacteric symptoms relief. Besides it is associated with the improved bone density and decreased risk of osteoporotic fractures [4]. That issue seem to be extremely important in the group of kidney graft recipients since long period of hemodialysis as well as long-term therapy with glicocorticosteroids put those women at high risk of osteoporosis development.

Transplant women from the study group reported effective relief of climacteric symptoms with associated improvement of life quality. According to the results of randomized trials the decrease in risk of endometrial cancer, colorectal cancer and osteoporotic fractures was expected in the study group. However, the benefits were supposed to be accompanied by the increase in risk of cardiovascular events, stroke and breast cancer, thus regular attentive follow-up was needed in patients receiving HRT. It should be emphasized, however, that the WHI trail did not take into account the effects of HRT in women under 60, therefore HRT use in younger patient does not have

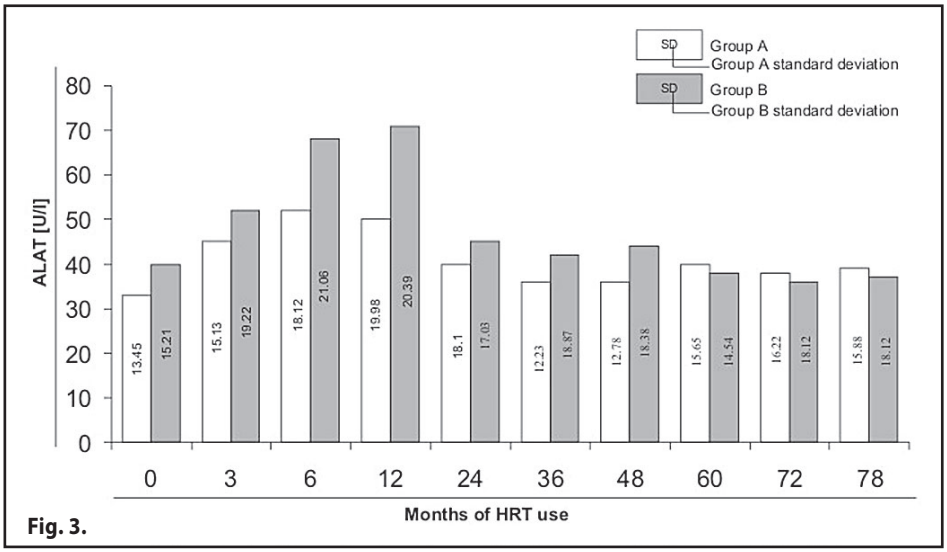

Fig. 3. Serum alanine aminotransferase (ALAT) concentration of HRT in kidney transplanted women.

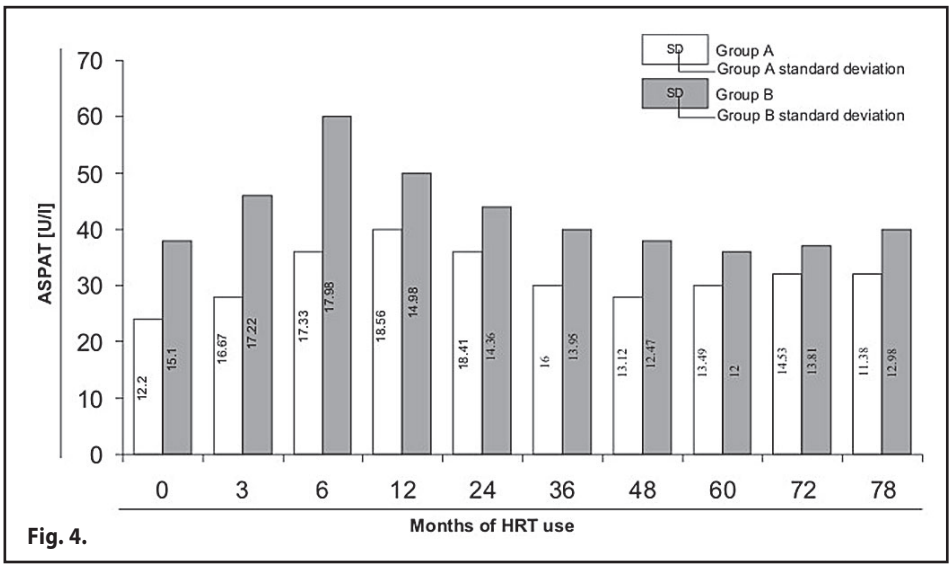

Fig. 4. Serum asparagine aminotransferase (ASPAT) concentration on HRT in kidney transplanted women.

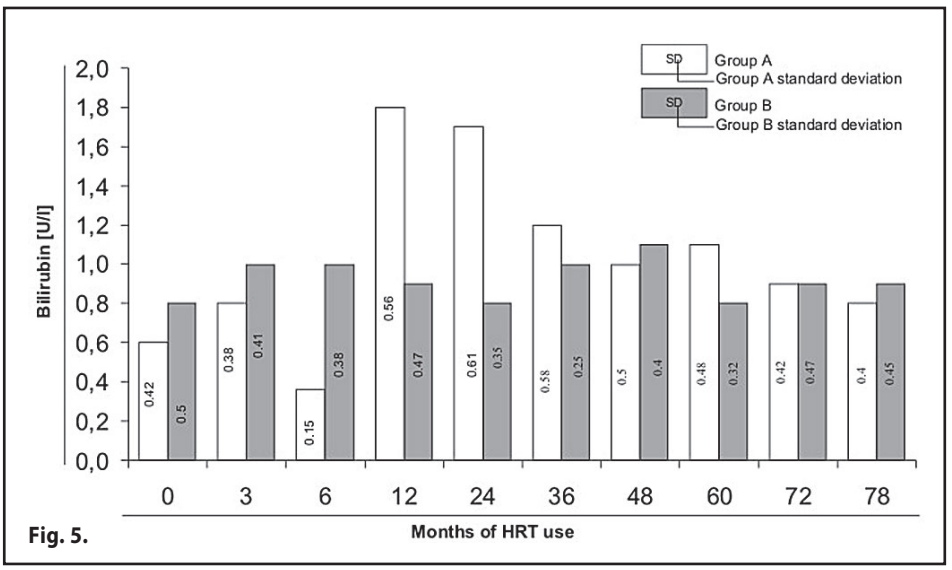

Fig. 5. Serum bilrubin concentration on HRT in kideny transplanted women.

to be associated with the above mentioned additional risks [5].

Graft recipients are used to visiting doctors regularly and seem to be relatively easy group of patients to cooperate. Frequent monitoring of the blood parameters of organs involved in hormonal drugs metabolism throughout the whole time of the therapy is essential. HRT was observed to deteriorate liver function and not to influence on kidney function in both groups of patients from the study group. 30% of women receiving transdermal-oral regimen and 22% of patients receiving transdermal regimen had to discontinue therapy for significant increase of ASPAT, ALAT and total bilirubin. In five women from that group, however, active Cytomegalovirus or Herpes Simplex Virus infection was detected, and liver parameters improved soon after the appropriate treatment had been administered. In case of the initial slight abnormalities in liver parameters, due to the lack of the hepatic first-pass effect, the transdermal route of administration was chosen. Transdermal route of HRT with the individualized strategy of using the minimum effective doses and optimal schedule (sequential versus continuous) is believed to become the route of choice in transplant patients who carry other risk factors of liver function deterioration: long-term immunosuppressive treatment and high rate of viral infections.

In conclusion, kidney transplanted women seem to benefit from hormonal replacement therapy that effectively relieves climacteric symptoms and improves life quality. In reflect of the possible risks associated with that kind of therapy, careful qualification and attentive surveillance is strongly recommended.

Conclusions

1. Most kidney transplanted women benefit from hormonal replacement therapy and experience significant relief of climacteric symptoms as soon as three months after the therapy onset.
2. There is the need for frequent attentive follow-up examinations and careful monitoring of both kidney and liver function parameters.
3. Deterioration of liver function is the most commonly observed side effect of HRT in female kidney recipients.
4. Further investigations on HRT use in kidney transplanted women are necessary to establish optimal dose, schedule and route of the therapy administration.

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