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Serum sex hormones concentrations in young women in the early period after successful kidney transplantation

Stężenie hormonów płciowych w surowicy u młodych kobiet we wczesnym okresie po zakończonym powodzeniem przeszczepieniu nerki

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Abstract

Background: Hormonal disorders are frequently present in haemodialysed patients with chronic kidney disease (CKD). In women with CKD sex hormone abnormalities may lead to irregular, often anovulatory cycles, sexual dysfunction, and infertility. Kidney transplantation (KTx) in young women tends to ameliorate most of the aforementioned disorders and improve fertility. The aim of this study was to assess the changes of serum sex hormone concentrations in young women before and six months after successful KTx

Materials and methods: Fourteen chronic haemodialysis women with CKD undergoing kidney transplantation and 46 apparently healthy women in similar age (control group) were enrolled into the study. In all women serum concentrations of FSH, LH, PRL, and oestradiol were determined. Measurements in the transplanted group were done four times: immediately before surgery, in the 14th and 30th day, and six months after the transplantation. The results are presented as means and 95% CI.

Results: All of the women that completed the study presented excellent function of the transplanted kidney — mean serum creatinine concentration was 92.54 (74.85–110.23) μmol/l. After successful KTx a significant decrease in the serum concentrations of FSH and LH was observed. The decrease of serum PRL concentration after KTx did not reach statistical significance in the multiple comparisons analyses but returned to the values observed in healthy controls. KTx did not significantly influence serum oestradiol concentration.

Conclusions: Successful kidney transplantation leads to the normalisation of serum concentrations of hormones linked to fertility disorders in women with chronic kidney disease. **(Endokrynol Pol 2018; 69 (2): 150–155)**

Key words: *chronic kidney disease, kidney transplantation, sex hormones*

Streszczenie

Wstęp: U chorych z przewlekłą chorobą nerek (*chronic kidney disease*, CKD) poddawanych hemodializie często obserwuje się zaburzenia hormonalne. U kobiet z CKD nieprawidłowe stężenia hormonów płciowych mogą powodować nieregularne, często bezowulacyjne cykle, zaburzenia czynności seksualnych i bezpłodność. Po przeszczepieniu nerki u młodych kobiet zwykle następuje złagodzenie większości z tych zaburzeń i poprawa płodności. Badanie przeprowadzono w celu oceny zmian stężeń hormonów płciowych w surowicy oznaczonych przed i po udanym przeszczepieniu nerki.

Materiały i metody: Do badania włączono 14 przewlekle hemodializowanych kobiet z CKD, u których planowano przeszczepienie nerki oraz 46 zdrowych kobiet w podobnym wieku (grupa kontrolna). U wszystkich kobiet oznaczono stężenia w surowicy hormonu folikulotropowego (*follicle-stimulating hormone*, FSH), hormonu luteinizującego (*luteinizing hormone*, LH), prolaktyny (*prolactin,* PRL) i estradiolu. W grupie poddanej transplantacji pomiary wykonano 4-krotnie: bezpośrednio przed zabiegiem, w 14. i 30. dobie po zabiegu oraz 6 miesięcy po zabiegu. Wyniki przedstawiono jako średnie i 95-procentowe przedziały ufności.

Wyniki: U wszystkich kobiet, które ukończyły badanie stwierdzono bardzo dobrą czynność przeszczepionej nerki — średnie stężenie kreatyniny w surowicy wynosiło 92,54 (74,85–110,23) μmol/l. Po udanym przeszczepieniu nerki zaobserwowano istotne zmniejszenie stężeń w surowicy FSH i LH. Zmniejszenie stężenia PRL w surowicy po przeszczepieniu nerki nie osiągnęło poziomu istotności statystycznej w testach wielokrotnych porównań, ale stężenie tego hormonu wróciło do wartości obserwowanych u zdrowych osób z grupy kontrolnej. Przeszczepienie nerki nie wpłynęło istotnie na stężenie estradiolu w surowicy.

Wnioski: Zakończone powodzeniem przeszczepienie nerki powoduje normalizację stężeń w surowicy hormonów związanych z zaburzeniami płodności u kobiet z CKD. **(Endokrynol Pol 2018; 69 (2): 150–155)**

Słowa kluczowe: *przewlekła choroba nerek, przeszczepienie nerki, hormony płciowe*

Introduction

Disturbances of function of most endocrine glands are common in patients with chronic kidney disease (CKD). The aetiology of such disturbances is diverse and may arise from the impaired production, secretion, or metabolism of various hormones by dysfunctional kidneys [1–4].

Disturbances of the hypothalamic–pituitary–ovarian axis occur early in the course of CKD and tend to progress after the initiation of haemodialysis or peritoneal dialysis [5–9]. In CKD women the loss of

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pulsatile gonadotropin secretion in the hypothalamus occurs, which leads to disturbances in the cyclic release of gonadotropins from the pituitary gland [7, 10–12]. This is why the regularity of serum follicle-stimulating hormone (FSH), luteinising-hormone (LH), and ovarian steroids fluctuations, typical for a normal menstrual cycle, are disrupted.

Young CKD female patients present normal, or more often slightly elevated basal serum LH concentration, but the pre-ovulatory peak of serum LH concentration is blunted [5, 7]. Serum FSH concentrations in haemodialysed women are usually normal [6, 13–15], thus the serum LH/FSH ratio is commonly increased. In young women with CKD the impairment of hormonal function of the ovaries may lead to the reduction in serum oestrogen concentration [5, 7]. Thus, in haemodialysed CKD women under 40 years of age, primary ovarian insufficiency is more common than in the general population [16] and menopause occurs 4.5 years earlier than in healthy women [9, 17].

The alterations of the inhibition of pituitary gland hormone secretion leads to overproduction of prolactin (PRL) and impaired diurnal rhythm of PRL release [9, 16, 18]. Hyperprolactinaemia is common in CKD; it occurs in about 70% women in CKD stage 5 [19]. This is due to the aforementioned overproduction, reduced metabolism, and decreased excretion of PRL by the kidneys [19, 20]. Increased serum PRL concentration is one of the major factors contributing to the dysregulation of the hypothalamic–pituitary–ovarian axis in these patients.

Hormonal disturbances observed in females receiving renal replacement treatment are the cause of irregular, usually anovulary menstrual cycles and concomitant fertility disorders [5, 16, 21]. Moreover, even in women with preserved ovulation, the luteal phase is often shortened [7, 22].

All of the aforementioned endocrine disturbances and concomitant disorders in sexual functions (e.g. less frequent sexual intercourse and loss of libido) in women with CKD lead to the impairment of fertility, which is most pronounced in stage 5 of CKD [23, 24]. Pregnancy is rare in haemodialysed females — its prevalence being 0.3/100 females/year, which is 40 times less common than in the general population. Kidney transplantation (KTx) is the treatment of choice in patients with terminal renal failure and usually leads to the reduction of the disturbances of the menstrual cycle [10–12], as well as the improvement of fertility [20, 25, 26]. In about 60% of women after successful KTx regular menstrual cycles are observed, while only 30% of women receiving renal replacement treatment have regular menstrual cycles [26, 27]. Pregnancy is four times more common in woman after KTx than in women on haemodialysis. Nevertheless, this is still about 10 times less frequent than in the general population [20].

There have been very few studies conducted so far that prospectively assess the serum sex hormone concentrations in young women immediately before and after kidney transplantation (KTx). Thus, the aim of this study was to assess the serum concentration of these hormones in women with terminal renal failure requiring renal replacement treatment and then again in the early period after successful KTx.

Materials and methods

Fourteen young women with CKD stage 5D (age 18–40 years) treated with haemodialysis or peritoneal dialysis were enrolled into the study (study group). Additionally, 46 apparently healthy women in similar age were enrolled into this study as a control group. None of the enrolled women used hormonal replacement therapy or oral contraception, exogenous glucocorticoids, or any medication that could influence the serum PRL concentration within the three months preceding enrolment. No history of thyroid diseases was present in 9 of 10 subjects enrolled to the study, and their thyroid stimulating hormone (TSH) concentration assessed during the tests necessary before the application to the transplantation program, was within the normal ranges. One of the enrolled women was on levothyroxine substitution and was euthyreotic pre- and postoperatively.

All women from the study group underwent a deceased-donor kidney transplantation. During the observation period four of the enrolled women were excluded from the follow-up due to loss of the transplanted kidney function during the first two months after the surgery.

Eight of the 10 remaining subjects were treated before kidney transplantation with haemodialysis (among them seven had arterio-venous shunt as a vascular access for haemodialysis and one had a permanent venous catheter), and two females were treated with continuous ambulatory peritoneal dialysis (CAPD). Two of the 10 females who finished the study had a kidney transplanted for the second time (re-transplantation), and for the remaining eight it was the first transplantation procedure.

The aetiology of CKD in this group was: chronic glomerulonephritis (four cases), diabetic nephropathy (two cases), vasculitis (one case), polycystic kidney disease (one case), and Alport's syndrome (one case). Six of the women who finished the study were previously pregnant, among them one female more than once. Four of the pregnancies ended with a miscarriage, and in one case it was during the renal replacement treatment.

A meticulous medical history (including menstruation and fertility disorders, number of pregnancies, and the actual day of the menstrual cycle during the examination) was obtained from all of the enrolled women from both the study group and the healthy controls. Menstrual cycles lasting 29 ± 3 days were regarded as regular. A lack of menstrual bleeding for more than six months was classified as amenorrhoea.

In the study group, blood samples for laboratory analyses were collected four times: just before the procedure, in the 14th and 30th day after the surgery, and then six months after the transplantation. In the healthy controls, blood samples for analysis were collected once — the sample collection was in the follicular or luteal phase. Blood samples were not collected during ovulation. After collection, blood samples were centrifuged, aliquoted, and stored at –70°C until assay.

In all patients the serum creatinine concentration was measured using a Beckman-Coulter UniCel DxC 600 analyser. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula. Albumin and high-sensitivity C-reactive protein (CRP) concentrations were measured by ELISA: albumin — Assaypro LLC, St. Charles, USA; CRP — Immundiagnostik AG, Bensheim, Germany). Serum concentrations of FSH, LH, PRL, and oestradiol were assessed using an ECL assay (Roche Diagnostics, Mannheim, Germany).

The intermediate precision for the PRL assay was 2.8–5.0%, and the measuring range was 1–10,000 μIU/ml. The respective values for the oestradiol assay were 4.3–9.9% and 5.0–4300.0 pg/ml (functional sensitivity 12 pg/ml). For FSH assay the intra assay coefficient of variation (CoV) was 1.5–1.8% and the intermediate precision was 3.8–5.3%; the measuring range was 0.1–200.0 mIU/ml. For the LH assay the respective values were: 0.8–1.8% and 2–5.2% and 0.1–200.0 mIU/ml.

The study protocol, adherent to the declaration of Helsinki, was approved by the Ethics Committee of the Medical University of Silesia (KNW/0022/KB1/81/11 and KNW/0022/KB1/82/11), and all patients gave informed, written consent for participation in the study. The study was supported by a research grant from the Medical University of Silesia — contract number: KNW-1-196/N/5/0.

Statistical analyses

Statistical analyses were performed using the following software: Statistica 10.0 PL (Statsoft Polska, Cracow, Poland) and PQStat (PQStat Software, Poznan, Poland). The Shapiro-Wilk test was used to assess the distribution of variables. Because most of the analysed variables presented skewed distribution, non-parametric tests were used. The statistical significance of the differences between groups was assessed using the Mann-Whitney U-test, and longitudinal analyses were performed using Friedman's ANOVA with Dunn post-hoc correction for multiple comparisons. Results are presented as means with 95% confidence interval, and the differences were considered significant when $p < 0.05$

Results

A significant decrease in the creatinine concentration after successful kidney transplantation was observed. The decrease in serum creatinine concentration reached the level of significance (after a correction for multiple comparisons) a month after the procedure (Table I). The eGFR values on the 14th and 30th day and six months after transplantation were 56.1 (39.6–72.7) ml/min/1.73 m^2, 65.1 (49.4–80.8) ml/min/1.73 m^2, and 69.0 (54.9–83.1) ml/min/1,73 m^2, respectively.

Moreover, a significant ($p = 0.034$) decrease of serum CRP concentration and increase of serum albumin concentration ($p = 0.008$) after KTx was found (Table I).

During the observation period the serum concentration of both the LH and FSH decreased significantly (Table I). This is why there were no significant changes observed in the FSH/LH ratio during the study period. The serum concentration of PRL was lower at the end of the study than at the beginning of the observation, but the difference did not reach statistical significance after correction for multiple comparisons (Table I). Moreover, there was no significant difference in the oestradiol concentration during the study period.

As far as regular menstruation is concerned, before the procedure five women had regular menstrual cycles, and in the remaining five menses were irregular. Six months after the transplantation procedure regular menstrual cycles returned in three women, thus only two out of the 10 subjects had irregular menstrual cycles (Table II).

In the analyses comparing the study group and the control group no differences in age and the time of first menstruation (Table II) were found. BMI was significantly lower in women before transplantation. Also, the irregularities of menstrual cycles were more common in the group of women with kidney failure (Table II).

Serum concentrations of urea, glucose, and triglycerides were significantly higher in the group before transplantation, in comparison to values obtained in healthy females ($p < 0.001$, $p = 0.014$, and $p < 0.001$, respectively — Table III). On the other hand, blood haemoglobin and serum total protein concentration were significantly lower in females from the study group before KTx ($p < 0.001$ and $p = 0.002$, respectively — Table III).

A comparison of the study group and healthy controls at baseline revealed clear differences in serum

Table I. *Serum concentrations of: creatinine, albumin, CRP, LH, FSH, PRL, and oestradiol in healthy women (control group) and in CKD women during the 6-month observation period after kidney transplantation. Statistical differences between study group and control group are presented in the text*

Tabela I. *Stężenia kreatyniny, albuminy CRP, LH, FSH, PRL i estradiolu w surowicy u zdrowych kobiet (grupa kontrolna) i kobiet z CKD w trakcie 6-miesięcznej obserwacji po przeszczepieniu nerki*

	Control group	Studied group				
		before KTx	14th day after KTx	30th day after KTx	6 months after KTx	p#
Creatinine [μmol/l]	59.90 (56.35–63.45)	536.32 (330.60–42.04)	140.93 (43.24–238.62)	102.81$ (69.45–136.17)	92.54$ (74.85–110.23)	< 0.001
Albumin [g/dl]	3.45 (3.27–3.63)	3.27 (2.85–3.69)	3.06 (2.61–3.51)	3.20 (2.86–3.54)	3.44 (3.12–3.76)	0.008
CRP [mg/l]	5.92 (3.99–7.84)	3.46 (1.26–5.66)	22.33 (from –5.78 to 50.44)	7.08 (from –0.12 to 14.28)	0.60 (0.21–0.99)	0.034
LH [mIU/ml]	7.29 (6.10–8.49)	17.77 (11.04–24.50)	10.99 (2.71–19.27)	12.75 (4.43–21.07)	8.79 (5.50–12.08)	0.036
FSH [mIU/ml]	5.82 (5.17–6.47)	4.84 (4.36–5.32)	3.08* (2.35–3.81)	3.93 (2.64–5.22)	4.00 (3.09–4.91)	0.031
LH / FSH	1.38 (1.14–1.62)	3.65 (2.27–5.04)	3.31 (1.44–5.18)	2.91 (1.29–4.54)	2.26 (1.49–3.02)	0.564
PRL [μIU/ml]	369.70 (312.25–427.14)	875.80 (103.20–1648.40)	541.70 (106.23–977.17)	407.30 (261.94–552.66)	355.1 (188.13–522.07)	0.095
Oestradiol [pg/ml]	112.00 (78.94–145.06)	145.10 (67.30–222.90)	140.70 (8.99–272.41)	154.80 (13.56–296.04)	141.30 (95.31–187.29)	0.392

*p < 0.05 *vs.* before transplantation
$p < 0.001 *vs.* before transplantation
#p for ANOVA in the study group
KTx — kidney transplantation, LH — luteinizing hormone, FSH — foliculotropic hormone, PRL — prolactin

creatinine concentration (p < 0.001). The studied group was also characterised by higher serum concentration of CRP and lower albuminaemia (p = 0.02 and p < 0.001, respectively — Table I).

As far as the concentration of serum hormones is concerned, no significant differences in the serum concentrations of oestradiol and FSH between the groups were observed (p = 0.36 and p = 0.2, respectively). Nonetheless, the studied group presented significantly higher serum PRL and LH concentrations (p = 0.046 and p < 0.001, respectively). Also, the LH/FSH ratio was significantly higher in the studied group than in the control group (Table I).

A comparison of the study group and healthy controls done six months after successful KTx revealed persisting differences in serum creatinine concentrations (p = 0.008). On the other hand, after the half-year observation period the studied group was characterised by lower serum CRP concentration (p = 0.036 — Table 1). There were no significant differences in albuminaemia found between the groups after the six-month observation period (p = 0.08).

There were no significant differences in the serum concentration of oestradiol between the controls and women after KTx at the end of the observation period. Conversely, a significantly lower serum FSH concentration in the transplanted women was observed (p = 0.02 — Table I). Additionally, no significant differences between the groups in the serum PRL or LH concentration was seen (p = 0.3 and p = 0.36 — Table III). Nevertheless, the LH/FSH ratio was significantly higher in the studied group than in the control group.

Discussion

Several different disorders of the endocrine glands are observed in patients with CKD, including deregulation of the hypothalamic — pituitary — ovarian axis [2, 5–8, 13].

The normalisation of sex hormone secretion after successful kidney transplantation leads to the correct Graafian follicle maturation, ovulation, and luteinisation. Moreover, it leads to the improvement of the concentration profile of sex hormones due to the

Table II. *Basic characteristics of the studied and control groups*

Tabela II. *Podstawowa charakterystyka grup badanej i kontrolnej*

	Studied group (n = 10)	Control group (n = 46)	p
Age [years]	34.1 (31.4–36.8)	31.3 (29.5–33.1)	0.23
Time since first menstruation [years]	20.0 (16.7–23.2)	17.9 (16.0–19.8)	0.17
Irregular menstruation cycles [number of patients/%]	5/50%	6/13%	0.03
Time since the diagnosis of CKD [years]	13.9 (6.2–21.5)	n/a	
Mode of renal replacement treatment before KTx [number of patients/%]	8/80%	n/a	
haemodialysis peritoneal dialysis	2/20%		
Time since the introduction of renal replacement treatment [months]	28.6 (11.4–45.8)	n/a	
BMI [kg/m^2]	19.7 (18.8–20.6)	22.6 (21.3–24.0)	0.02
Systolic blood pressure [mmHg]	136.0 (123.3–148.7)	115.6 (110.8–120.5)	< 0.001
Diastolic blood pressure [mmHg]	83.5 (74.6–92.4)	74.1 (70.2–78.1)	0.02

BMI — body mass index, CKD — chronic kidney disease, KTx — kidney transplantation, n/a — not applicable

Table III. *Blood haemoglobin concentration and serum creatinine, urea, glucose, total cholesterol, triglycerides, and total protein concentration in females before kidney transplantation (studied group) and in healthy controls*

Tabela III. *Stężenie hemoglobiny we krwi oraz kreatyniny, mocznika, glukozy, cholesterolu całkowitego, trójglicerydów i białka całkowitego w surowicy u kobiet przez przeszczepieniem nerki oraz w grupie kontrolnej*

	Studied group (n = 10)	Control group (n = 46)	p
Haemoglobin [g/dl]	11.03 (10.26–11.80)	12.89 (12.48–13.31)	< 0.001
Urea [mmol/l]	14.97 (12.90–17.04)	4.61 (4.25–4.98)	< 0.001
Glucose [mmol/l]	6.22 (3.74–8.71)	4.45 (4.25–4.65)	0.014
Total cholesterol [mmol/l]	5.18 (4.30–6.06)	4.68 (4.42–4.93)	< 0.001
Triglycerides [mmol/l]	1.59 (1.31–1.88)	0.79 (0.66–0.92)	< 0.001
Total protein [g/dl]	5.96 (5.18–6.74)	7.04 (6.89–7.20)	0.002

decrease of improperly elevated serum FSH, LH, and PRL concentrations and the increase of improperly lowered concentration of serum oestradiol (E_2). The serum concentrations of both E_2 and PRL in females with good function of transplanted kidney are comparable with those observed in apparently healthy women [10, 25]. Most probably due to the normalisation of serum PRL concentration after kidney transplantation, the pulsatile rhythm of FSH and oestrogen secretion returns to values close to normal, also a decrease in secretion of LH is observed.

As shown previously, in about 68% of women after successful KTx regular menstrual cycles occur, which is similarly frequent as in the general population [11, 25, 26]. This is also in agreement with the results of the current study in which over 80% of females had regular menstrual cycles after the six-month observation period.

Successful kidney transplantation tends to ameliorate the hormonal disturbances that occur in the course of CKD [10–12, 26–28]. One of the most important findings in the endocrine balance in females after KTx is the decrease of improperly elevated in uraemia serum concentrations of LH and FSH [10, 12, 26, 27]. This is mostly in agreement with the results of our study, in which also a significant decrease of serum FSH and LH concentrations have been found. As far as serum LH concentration is concerned the baseline concentration was markedly higher in women awaiting the KTx and after six months. On the other hand, while the serum FSH concentration dropped, as predicted after the KTx, it was initially not significantly different from the serum FSH seen in the healthy controls. The difference became apparent after KTx, which caused the decrease of serum FSH concentration. Additionally, as both LH and FSH concentrations dropped to a similar extent, no significant differences in the FSH/LH ratio was seen in our study population pre- or post-KTx. The ratio was persistently significantly higher than in healthy controls.

Hyperprolactinaemia is often observed in women with CKD, as a result of the excessive production, decreased metabolism, and impaired excretion of PRL by the kidneys [1, 7, 9, 13, 16, 18, 19, 29]. The prevalence of hyperprolactinaemia increases along with the reduction of glomerular filtration and is most common in stage 5 of CKD. Despite the fact that, as mentioned before, successful KTx tends to ameliorate most of the hormonal disturbances linked to uraemia, there were no significant differences but only a trend (p = 0.09) towards lower serum PRL concentration after KTx was found.

This seems to be in contrast to some previous studies [12, 27, 30] but is probably caused by the modest number of enrolled patients and by the conservative statistical methods used in our study. Of note, even though the decrease of PRL did not reach significance the serum PRL concentrations found in women six months after KTx were no different from the serum PRL obtained from the healthy controls.

In the current study no significant differences were found in the serum oestradiol concentrations between the haemodialysed woman and the control group. This is in agreement with the results of previous studies concerning this topic [13, 15, 27].

Among the drawbacks of our study the modest number of patients enrolled to the study group should be mentioned. This of course precluded the significance of any correlation analyses. The size of the study group arises from the fact that a young woman is not a typical patient requiring renal replacement therapy. Also, women using hormonal contraception were not enrolled. It is worth mentioning, however, that even in this small group some significant differences of serum hormone concentrations were obtained.

In conclusion, we found that successful kidney transplantation leads to the normalisation of serum concentrations of the majority of hormones linked to fertility disorders in chronic kidney disease.

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