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Original Paper

Serum Anti-Müllerian Hormone Concentration in Young Women with Chronic Kidney Disease on Hemodialysis, and After Successful Kidney Transplantation

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Key Words
Anti-Müllerian hormone • Chronic kidney disease • Hemodialysis • Kidney transplantation

Abstract
Background/Aims: In women with chronic kidney disease (CKD) fertility abnormalities occur frequently. Anti-Müllerian hormone (AMH) inhibits excessive recruitment of primordial follicles. The aim of the study was to evaluate the serum AMH concentration in women on hemodialysis and after kidney transplantation (KTx). ***Methods:*** 46 hemodialysed women and 14 with CKD about to undergo kidney transplantation were enrolled into the study. The control group consisted of 40 healthy women. In all subjects serum concentration of AMH was determined (in chronic hemodialysis women and in control group once, and in women after KTx immediately before surgery, and 3 times after the transplantation). ***Results:*** Serum AMH concentration in hemodialysed women and in the control group did not differ significantly, while in hemodialysed women with regular menstrual cycles it was significantly lower than in the control group: 2.20 (1.08-3.55ng/ml) and 3.30 (1.80-6.10ng/ml) respectively, (p=0.02). In the KTx group, a significant decrease in serum AMH concentration was found from 3.30ng/ml (2.20-6.50ng/ml) at baseline to 1.90ng/ml (1.30-2.40ng/ml) at 6 months after KTx (p=0.007). ***Conclusions:*** 1. Significantly lower serum AMH concentration was found in the regularly menstruating CKD women on hemodialysis in comparison with the healthy controls. 2. Serum AMH decreased significantly after successful KTx.

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Introduction

Disturbances of function of many endocrine glands are common in patients with chronic kidney disease (CKD) and their etiology is complex. Such disturbances may be caused by impaired production, secretion, or metabolism of various hormones by dysfunctional kidneys [1, 2]. Disturbances of the hypothalamic–pituitary–ovarian axis occur early in the course of CKD and tend to progress after the initiation of renal replacement therapy. However, successful kidney transplantation (KTx) ameliorates the severity of many hormonal disorders in patients with CKD [3-5].

In hemodialysed women aged less than 40 years primary ovarian insufficiency is more common than in the general population [6]. Menopause occurs in these women 4.5 years earlier than in healthy women [1, 7].

Hormonal disturbances observed in women receiving renal replacement therapy are the principal cause of irregular, usually anovulatory menstrual cycles and concomitant infertility [2, 6-8]. Even in women with preserved ovulation, the luteal phase is often shortened. Complete amenorrhea in women with uremia is less common [9, 10].

All of the aforementioned endocrine disturbances and concomitant disorders of sexual function (e.g. reduction in frequency of sexual intercourses and loss of libido) in women with CKD lead to fertility impairment, which is most pronounced in CKD stage 5 [1, 6]. Pregnancy is rare in hemodialysed women – its prevalence is 0.3/100-women/year, which is 40 times less than in the general population [11].

Kidney transplantation usually improves menstrual cycle disturbances and increases fertility [12, 13]. In 60% of women after successful KTx, regular menstrual cycles return, compared to only 30% of women having regular menstrual cycles while receiving renal replacement therapy [2, 13]. Pregnancy is four times more common in women after KTx than in hemodialysed women, but is still about 10 times rarer than in the general population. The normalization of sex hormones secretion after successful KTx leads to normal Graafian follicle maturation, ovulation and luteinization.

Anti-Müllerian hormone (AMH) is a 140 kDa glycoprotein [14]. In women, it is synthesized by the granulosa cells of primary, preantral and small antral follicles, until they reach the diameter of 6-8 mm [15]. The highest serum AMH concentrations are observed during puberty. The main function of AMH in folliculogenesis is the inhibition of excessive recruitment of primordial follicles and modification of the preantral and antral follicles growth by the reduction of their sensitivity to stimulation by FSH [14, 16].

Serum AMH concentration in women is not dependent on menstrual cycle phase and remains at a constant level during the entire cycle [15]. Serum AMH is positively correlated with the number of antral follicles and decreases with age at a rate of 6% per year until it is virtually undetectable in postmenopausal women. This is related to the decrease of the quantity of growing follicles [17-20]. Thus, serum AMH concentration reflects the pool of follicles and is considered the best marker of ovarian reserve. A decrease of serum AMH may indicate both physiological and premature aging of the gonads [17, 21].

The result of serum AMH assessment is crucial in the diagnostics of ovarian dysfunction. Primary ovarian damage leads to the increase of serum gonadotropins (hypergonadotropic hypogonadism) with concomitantly decreased serum concentrations of AMH and estradiol. The ovaries are prone to be injured by many factors because of the limited number of germinal cells and their inability to regenerate [21]. There are many theories trying to explain the eventual expiration of the ovarian function, such as: ischemia, oxidative stress, and also genetic, auto-immunologic or inflammatory factors. In previous studies decrease of AMH concentration has been observed as a result of oncological chemotherapy [19, 22-24]. Additionally, lower serum AMH concentrations are linked to obesity [25]. In women with CKD the aforementioned fertility disturbances may be caused by the damage of the ovaries by uremia, but no studies concerning the serum AMH concentration in women with CKD have been conducted so far. In contrast, higher than physiological serum AMH concentrations

have been reported mostly in women with polycystic ovaries syndrome (two- to three fold concentration elevation that reflects the load of growing follicles).

As it has been already mentioned, there are no published studies of serum AMH concentrations in women with CKD and after KTx. The aim of this study was to assess the serum AMH concentration in young women with CKD treated with hemodialysis, and in a similarly-aged cohort of women before and after successful KTx.

Subjects and Methods

Study groups

The study consisted of two independent parts.

In the first part, 46 women with a mean age of 32.1 years (30.5-33.8 years) with CKD treated by hemodialysis three times per week, for at least one month were enrolled into the study. The median hemodialysis period was 32.0 months (11.0-60.0 months), the median time since the diagnosis of CKD was 9.00 years (4.00-15.00 years and the median BMI was 21 kg/m^2 (20.00-23.25 kg/m^2). Mean time since first menstruation was 18.7 years (16.7-20.7 years) and the prevalence of irregular menstrual cycles was 54.4%.

The control group comprised 40 healthy women with regular menstrual cycles, without fertility disorders and of a similar age as the "hemodialysis" group (p=0.42). Mean age in this group was 31.1 years (29.1-33.0 years). Time since first menstruation was 17.7 years (15.6-19.8 years), which was not different from the hemodialysis group (p=0.49). The median BMI was 22.0 kg/m^2 (20.0-25.0 kg/m^2).

The exclusion criteria were: pregnancy, history of ovarian surgery, severe illness (other than uremia) with life expectancy shorter than 6 months, active infection, use of hormonal replacement therapy, or oral contraception within 3 months preceding enrollment.

The causes of CKD in the group receiving renal replacement therapy were: chronic glomerulonephritis (12 cases – 26.1%), diabetic nephropathy (8 cases – 17.4%), hypertensive nephropathy (4 cases – 8.7%), vasculitis (3 cases – 6.6%), reflux nephropathy, polycystic kidney disease, thrombotic microangiopathy (2 cases – 4.3% each), and other causes (6 cases – 6.6%: e.g. Alport's syndrome, tubule-interstitial nephritis, congenital urinary tract malformations). In 8 women (17.4%), the etiology of renal failure was unknown.

34 subjects (73.9%) had a patent arterio-venous fistula as vascular access for hemodialysis, 9 (19.6%) were dialysed using a permanent catheter and 3 (6.5%) using a temporary catheter. 9 patients had history of cyclophosphamide treatment (for glomerulonephritis) before they reached end-stage renal failure.

Twenty one patients (45.6%) of the hemodialysed group had previously been pregnant, 15 of them more than once. Thirteen pregnancies had ended in miscarriage and 4 of these miscarriages were after starting hemodialysis treatment. There were no successful pregnancies after women had started dialysis. In the control group (healthy women), 23 women (57.5%) had previously been pregnant, 18 of them more than once. Four pregnancies had ended in miscarriage.

The second part of the study was the prospective evaluation before, and in the early period after, successful KTx. Fourteen women with a mean age of 34.1 years (31.4-36.8 years) was enrolled into this part of the study. The median period of hemodialysis was 22.5 months (18.0-24.0 months), the median time since diagnosis of CKD was 11.5 years (4.0-24.0 years) and the median BMI was 19.0 kg/m^2 (19.0-21.0 kg/m^2). Mean time since first menstruation was 20.0 years (16.7-23.2 years) and the prevalence of irregular menstrual cycles was 50.0%. Four of the enrolled women were excluded from follow-up because of loss of transplant kidney function during the first 2 months after surgery.

The exclusion criteria were identical to those for hemodialysed women in the first part of the study. Eight of the 10 women were having a first KTx and the remaining 2 a second KTx.

The etiology of CKD in this group was: chronic glomerulonephritis (4 cases), diabetic nephropathy (2 cases), vasculitis (1 case), polycystic kidney disease (1 case) and Alport's syndrome (1 case). In one case the etiology of CKD was unknown.

Eight of 10 women in the KTx group were being treated with hemodialysis (7 had an arterio-venous fistula as vascular access for hemodialysis and 1 had a permanent catheter) and 2 women were being treated with peritoneal dialysis at the time of KTx. None underwent preemptive KTx.

In the KTx group, 6 women had previously been pregnant, one woman more than once. Four of the pregnancies had ended in miscarriage, and in one case it was after the start of renal replacement treatment. Immediately after KTx, immunosuppressive treatment consisted of prednisone, tacrolimus (Tac) and mycophenolate mofetil (MMF) in 7 women, and prednisone, cyclosporine A and MMF in 3 women. Six months after KTx it was prednisone, Tac and MMF in 6 women, Tac and MMF in 2 women and Tac and azathioprine in 1 subject.

The course of the study

A detailed medical history was obtained from all subjects (including menstruation and fertility disorders, number of pregnancies and the actual day of the menstrual cycle during the examination). Regular menstrual cycles were regarded as those lasting between 29 ± 3 days. The lack of menstrual bleeding for more than 6 months was classified as amenorrhea.

In the hemodialysed women, blood samples were collected once, before a hemodialysis session in the middle of the week. In the patients undergoing KTx, blood samples were collected four times: directly before the surgery, on the 14th and 30th post-operative days and 6 months after KTx. Patients whose KTx was lost during the 6-month observation period were excluded from the analysis. After collection, blood samples were centrifuged and frozen at -70^{o}C until assays were performed.

In the whole study population, blood hemoglobin concentration (XT 2000i analyzer, Sysmex, Japan), and serum creatinine, urea, glucose, total cholesterol, triglycerides and total protein concentrations were measured using the routine methods used in the Hospital's Central Laboratory (Beckman-Coulter UniCel DxC 600 analyser). In the women after KTx, serum creatinine concentration was assessed at every time point. In the healthy women (control group) and in the group after KTx, estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula.

In all subjects, 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 estradiol were assessed using an ECL assay (Roche Diagnostics, Mannheim, Germany). Serum free testosterone concentration was assessed using radioimmunoassay (DIAsource Immunoassays, Nivelles, Belgium) and serum inhibin-B and AMH using an ELISA kit (Beckman Coulter Inc., USA.) The intra-assay coefficient of variation for the AMH assay is 3.4-5.4% and the inter-assay coefficient of variation is 5.4-7.7%.

Ethics, consent and permissions

The study protocol, which conformed to the Declaration of Helsinki, was approved by the Medical University of Silesia Ethics Committee (KNW/0022/KB1/81/11 and KNW/0022/KB1/82/11). All patients gave informed, written consent to participation in the study.

Statistical analyses

Statistical analyses were conducted using: Statistica 10.0 PL (Statsoft Polska, Cracow, Poland) and PQStat (PQStat Software, Poznan, Poland). Shapiro-Wilk test was used to assess the distribution of variables. The differences between groups were assessed using Mann-Whitney U-test and the longitudinal (over time) analyses were performed using Friedman's ANOVA with Dunn post-hoc correction for multiple comparisons.

Results are presented as means with 95% confidence interval (for variables with normal distribution), or median values with interquartile range (for variables with skewed distribution), as appropriate. Differences with p <0.05 were considered significant.

Results

Women with CKD treated with hemodialysis and control group

There were no significant differences in age, time period since first menses and BMI between the hemodialysed and control groups (p=0.42; 0.49; 0.38, respectively). In the group of patients with CKD treated with hemodialysis compared to the control group, significantly higher serum concentrations of creatinine, urea, glucose, total cholesterol, triglycerides and

Table 1. Blood hemoglobin concentration and serum creatinine, urea, glucose, total cholesterol, triglycerides, total protein, albumin, CRP and AMH concentration in hemodialysed women with chronic kidney diseases and in the control group

	Hemodialysed group n = 46	Control group n = 40	*p*
Hemoglobin [g/dl]	10.70 (10.27 – 11.14)	13.00 (12.5-13.4)	<0.0001
Creatinine [µmol/l]	704.6 (628.6 – 780.6)	59.8 (56.1-63.5)	<0.0001
Urea [mmol/l]	20.42 (18.48 – 22.37)	4.53 (4.20-4.87)	<0.0001
Glucose [mmol/l]	5.54 (4.57 - 6.52)	4.53 (4.38-4.68)	0.009
Total cholesterol [mmol/l]	5.30 (4.80 - 5.79)	4.67 (4.38-4.95)	0.04
Triglycerides [mmol/l]	1.98 (1.70 - 2.25)	0.77 (0.63-0.90)	<0.001
Total protein [g/dl]	6.39 (6.07 - 6.71)	7.07 (6.91-7.24)	0.004
Albumin [g/dl]	3.45 (3.27 - 3.63)	4.05 (3.94-4.16)	<0.0001
median of CRP [mg/l]	3.45 (1.00-8.75)	0.95 (0.50-2.50)	0.004
median of AMH [ng/ml]	3.55 (1.80-5.80)	3.30 (1.80-6.10)	0.88

CRP = C-reactive protein, AMH = Anti-Muellerian hormone

Table 2. Serum LH, FSH, PRL, estradiol, testosterone and inhibin-B concentration in hemodialysed females with or without menstrual cycle abnormalities and in control group

	Hemodialysed women without menstruation cycle abnormalities (n=21)	Hemodialysed women with menstruation cycle abnormalities (n=25)	Control group (n=40)
LH [mIU/ml]	14.55 (10.86 – 18.24)	18.89 (10.81 – 26.96)	7.33 ** (6.01 – 8.65)
FSH [mIU/ml]	4.55 (3.75 – 5.35)	10.84 (-1.47 – 23.15)	5.65 ** (4.97 – 6.34)
LH / FSH	3.89 (2.42 – 5.37)	3.02 (1.98 – 4.06)	1.42 * (1.15 – 1.68)
PRL [µIU/ml]	858.05 (437.18 – 1278.92)	1392.84 (566.45 – 2219.23)	361.17 (302.02 – 420.32)
Estradiol [pg/ml]	91.48 (65.48 – 117.48)	93.76 (63.94 – 123.58)	122.22 (85.11 – 159.34)
Testosterone [ng/ml]	0.67 (0.46 – 0.87)	1.01 (0.75 – 1.26)	0.82 (0.7 – 0.94)
Inhibin-B [pg/ml]	58.05 (37.34 – 78.76)	97.12 * (69.40 – 124.84)	71.55 (57.79 – 85.31)

*p<0.05 vs. hemodialysed without menstruation abnormalities; **p<0.001 vs. hemodialysed without menstruation abnormalities; LH = luteinizing hormone, FSH = foliculotropic hormone, PRL = prolactin

CRP, but significantly lower serum concentrations of hemoglobin, total protein and albumin were found (table 1).

There was no significant difference in the serum AMH concentration between the hemodialysed and control groups – the median values were 3.55 (1.80-5.80ng/ml) vs 3.30 (1.80-6.10ng/ml) respectively; p=0.87. Additional hormonal data concerning the function of ovaries and pituitary are presented in table 2.

There was no significant difference in the serum AMH concentration between the women treated previously with cyclophosphamide and the rest of the hemodialysed women [2.60 (0.38-5.05ng/ml) vs 3.60 (1.95-6.63ng/ml), p=0.30].

The hemodialysed group was divided in two subgroups according to the regularity of menstrual cycles. Among 46 enrolled hemodialysed patients, 21 (45.6%) had regular menstruation and, the rest (54.4%), had menstrual abnormalities (19 women – 41.3% with irregular menstruation; 6 women – 13.1% with amenorrhea).

The analyses of the abovementioned subgroups revealed that hemodialysed women with regular menstrual cycles had significantly lower serum AMH concentrations than the healthy controls (p=0.02): median values were 2.20 (1.08-3.55ng/ml) vs 3.30 (1.80-6.10ng/ml), respectively. Moreover, in hemodialysed women with regular cycles, serum AMH concentration was significantly lower than in hemodialysed women with menstrual disorders: 2.20 (1.075-3.55ng/ml) vs 4.90 (3.10-8.85ng/ml), respectively, (p=0.001).

The difference in serum AMH concentration between healthy controls and hemodialysed women with menstrual disorders was not significant (p=0.07).

Table 3. Blood hemoglobin, and serum concentrations of creatinine, albumin and CRP during the 6-month observation period after kidney transplantation

	Before KTx (T_0)	14th day after KTx (T_1)	30th day after KTx (T_2)	6 months after KTx (T_3)	*p* for trend
Hemoglobin [g/dl]	11.03 (10.26-11.8)	10.04 (9.04-11.04)	11.37 (10.33-12.41)	12.6 (11.74-13.44)	0.11
Creatinine [μmol/l]	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]	3.27 (2.85 –3.69)	3.06 (2.61 – 3.51)	3.20 (2.86 – 3.54)	3.44 (3.12 – 3.76)	0.008
median of CRP [mg/l]	3.46 (0.80-6.38)	2.55 (2.30-28.8)	3.50 (0.50-10.4)	0.50 (0.20-0.70)	0.034

KTx = kidney transplantation, CRP = C-reactive protein; ***p < 0.001 *vs.* before transplantation

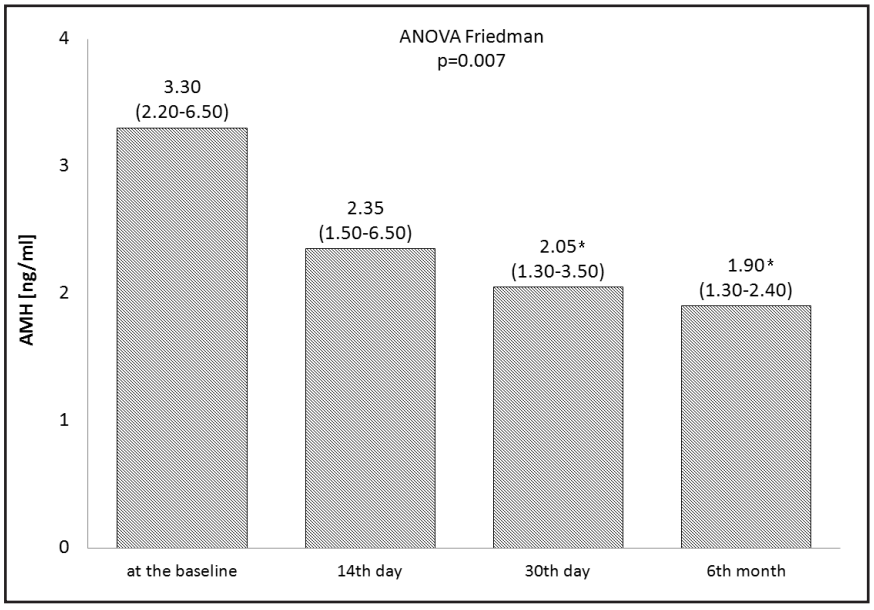

Fig. 1. Serum anti-Müllerian hormone (AMH) concentration in women in the early period after successful kidney transplantation (directly before kidney transplantation, and 14 days, 30 days and 6 months after the procedure). *p<0.05 vs baseline (after Dunn correction).

Women who underwent kidney transplantation (*KTx*)

In women before KTx, mean blood hemoglobin concentration was 11.03 (10.26–11.80 g/dl) and mean serum concentrations of urea, glucose, total cholesterol, triglycerides and total protein were: 14.97 (12.90–17.04 mmol/l); 6.22 (3.74–8.71 mmol/l); 5.18 (4.30–6.06 mmol/l); 1.59 (1.31–1.88 mmol/l) and 5.96 (5.18–6.74 g/dl), respectively.

There was a significant decrease in serum creatinine concentration after KTx (table 3). The eGFR on the 14th, 30th day and 6 months after KTx was 56.10 (39.55–72.66 ml/min/1.73m^2), 65.10 (49.41–80.78 ml/min/1.73m^2) and 69.00 (54.85–83.10 ml/min/1,73m^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 3). During the observation period, the serum AMH concentration decreased significantly (p=0.007) (figure 1).

Discussion

In this paper a study consisting of two independent parts is presented. The first part focused on hemodialysed young women with CKD. The second part involved young women before, and in the early period after, successful KTx. There were no significant differences in serum AMH concentration between the whole group of hemodialysed patients and the control group. However, serum AMH was significantly lower in hemodialysed women without menstrual disorders in comparison to the control group (figure 2). Significantly higher serum AMH concentration was found in haemodialysed women with CKD and

menstrual cycle abnormalities in comparison to those with regular menstrual cycles. In the group after KTx, a significant decrease in serum AMH concentration was observed as soon as 30 days post-KTx (figure 1). In the group of subjects 6 months after successful KTx, mean serum AMH was lower than in the control group.

Endocrine disturbances observed in hemodialysed women with CKD are the primary cause of irregular menstrual cycles and lack of ovulation [2, 9, 10, 26, 27]. Menstrual abnormalities are common in women with CKD and are most pronounced in CKD stage 5 [6, 10, 28]. Previously published studies showed a 42-75% prevalence of irregular menstrual cycles in hemodialysed women [13]. This is in agreement with the results of the current study – the percentage of irregular cycles in hemodialysed women was 54%. In previously published studies in the general population, longer and more irregular menstrual cycles were observed in women with elevated serum AMH concentrations [29]. In the current study, similar abnormalities occurred in hemodialysed women with CKD.

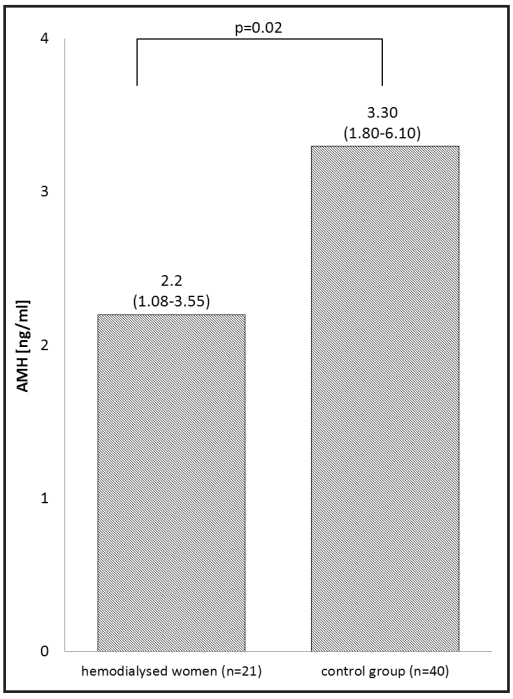

Fig. 2. Serum anti-Müllerian hormone (AMH) concentration in regularly menstruating hemodialysed women with chronic kidney disease and in the control group.

In the current study, the serum AMH concentration was significantly lower in the subgroup of regularly menstruating HD women than in the healthy controls. This might suggest a decrease of AMH secretion by the damaged granulosa cells and a reduction of ovarian reserve in CKD patients. To verify this hypothesis, an investigation of additional surrogates of ovarian reserve such as ovarian ultrasound examination and antral follicle count, should be conducted. Among hemodialysis patients serum AMH concentration was higher in women with irregular than in women with regular menstrual cycles. This is similar to the general population where increased serum AMH concentration is generally linked to polycystic ovaries syndrome (sometimes with only subclinical expression), hyperandrogenism, or others fecundity disorders [30]. Thus AMH is regarded as one of the best markers of ovarian reserve only in women with regular menstrual cycles. This is why only regularly menstruating women with CKD and general population have been compared in the current study.

Successful KTx tends to ameliorate the hormonal disturbances that occur in the course of CKD [13]. As it has been shown previously 55-73% of women after successful KTx have regular menstrual cycles, which is a similar frequency as in the general population [12, 31]. This was confirmed in the current study in which over 80% of women had regular menstrual cycles during the 6-month observation period.

AMH, similarly to other protein hormones, probably accumulates in CKD patients. The decrease in serum AMH 6 months after successful KTx suggests that serum AMH clearance is reduced in CKD patients. The possibility that immunosuppressive therapy (calcineurin inhibitors, mycophenolic acid derivatives and prednisone) used after KTx may decrease AMH secretion by damaging granulosa cells cannot be unequivocally excluded. However, it seems to be unlikely because a study by Mok C. et al. in patients with systemic lupus erythematosus, showed that none of these agents had any influence on serum AMH concentration [32].

The above described results concerning serum AMH concentration cannot be compared with results obtained by other authors because, to the best of our knowledge, no other

studies of this precise topic have been conducted so far. Because of the modest number of enrolled patients and the homogeneity of the hemodialysis and control groups, correlation analyses have not been conducted in the current study. Also, because of logistic difficulties, intravaginal ultrasound examination and antral follicle count could not be performed.

Conclusion

Summing up, in the current study no significant differences were found between serum AMH concentrations in young hemodialysed women with CKD and control patients. However, significantly lower serum AMH concentration was found in the subgroup of regularly menstruating hemodialysed women in comparison with the healthy controls. Moreover, results of the study showed a significant decrease of serum AMH concentration in women after successful KTx. The results of current study may suggest that ovarian reserve could be reduced in CKD patients. Further clinical and experimental studies are required to verify this hypothesis.

Disclosure Statement

The authors declare no conflict of interest

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