NEPHROLOGY - ORIGINAL PAPER

Ovarian reserve in an Egyptian cohort with end-stage kidney disease on hemodialysis and after successful kidney transplantation: a prospective study

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Abstract

Background Women with chronic kidney disease commonly have menstrual irregularities and fertility abnormalities. Antimüllerian hormone (AMH) and antral follicle count (AFC) are well-recognized indicators of ovarian reserve.

Aims To assess AMH level and total AFC in women who are on hemodialysis and after successful kidney transplantation (KTx).

Methods Sixty women with end-stage kidney disease (ESKD) on regular hemodialysis were included in this study with 20 patients of them were going to have renal transplant. Fifty age-matched healthy females were enrolled as control. Serum AMH level was measured in all participants once and in transplant patients four times (before surgery, and at 1, 6, and 12 months after surgery). AFC was evaluated once in all subjects and in transplant patients twice (before and 1 year after surgery).

Results ESKD patients had significantly lower AMH concentration and AFC than healthy controls (1.8 ± 1.2 vs. 3.5 ± 1.7 ng/ml, $p < 0.001$) and (12 ± 4.6 vs. 17.4 ± 4.3, $p < 0.001$), respectively. In the subgroup transplant patients, AMH level decreased significantly from (1.7 ± 1.3 ng/ml) before Ktx to (1.5 ± 1.2 ng/ml, $p = 0.001$) at 1 month, (1.1 ± 0.9 ng/ml, $p < 0.001$) at 6 months, (0.9 ± 0.8 ng/ml, $p < 0.001$) at 1 year after Ktx. Also, total AFC declined in transplant females from (11.1 ± 4.5) before KTx to (6.6 ± 3.4) after KTx ($p < 0.001$).

Conclusions Women with ESKD who are on hemodialysis have lower ovarian reserve than healthy females. Moreover, renal transplantation was associated with reduction in AMH level and AFC.

Keywords Antimüllerian hormone · Antral follicle count · Chronic kidney disease

Introduction

Women with chronic kidney disease (CKD) have many endocrinal disturbances which lead to ovarian dysfunction and reduction in their fertility. Menstrual irregularities and anovulatory cycles are commonly encountered problems in patients with end-stage kidney disease (ESKD) [1, 2]. Furthermore, women receiving hemodialysis for ESKD frequently have premature menopause [3].

The degree of fertility impairment seems to be related to the stage of CKD, which is most evident in ESKD [4]. Even in women on hemodialysis, the probability of achieving pregnancy is significantly lower than in the general population with some studies reported a pregnancy rate of 2.4% in this group of patients [5].

Renal transplantation was found to regulate the hormonal disturbances in patients with CKD with concomitant increase in the number of ovulatory cycles and improvement in the pregnancy rate [6]. In spite of that, women after kidney transplantation (KTx) still have significantly lower conception rate than in the general population [7]. This may indicate the presence of factors other than hormonal disturbances that reduce fertility in women who underwent KTx.

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Ovarian reserve is a major determinant of fertility in females of reproductive age. Ovarian aging is affected by many factors including medical, lifestyle, genetic, autoimmune aspects, and it could be idiopathic [8]. Many factors such as accumulation of uremic toxins and inflammation in CKD patients may cause ovarian damage and restricted quantity of ovarian follicular pool and lack of regenerative capacity.

Assessment of ovarian reserve can be obtained by measurement of biochemical and ultrasound methods [9]. Anti-müllerian hormone (AMH), a glycoprotein secreted by growing ovarian follicles, has a constant level throughout the menstrual cycle [10]. AMH has been considered as a marker of ovarian reserve and its level decreases with age [11]. Two recent studies demonstrated that patients with CKD have lower levels of AMH than age-matched healthy women [7, 12]. Moreover, AMH concentration was found to decrease after successful KTx [7]. Although AMH is an indicator of ovarian function, AMH expression and serum levels can be altered by many genetic and environmental factors [13].

Ovarian antral follicles can be identified and counted by transvaginal ultrasound [14]. Antral follicle count (AFC) is a non-invasive, easily performed technique that can be used as a surrogate marker for ovarian reserve [15, 16]. To our knowledge, no previous study evaluated AFC in hemodialysis women and after KTx. The aim of this study was to assess the serum AMH concentration and AFC in women with ESKD treated with hemodialysis and after successful KTx.

Subjects and methods

The patients were enrolled from the dialysis unite of a tertiary care hospital.

Cairo University Hospital is a major hospital and a tertiary referral center serving patients from Cairo and also patients referred from all other governorates of Egypt. This prospective study included 60 women with ESKD on regular hemodialysis for at least 3 months between July 2015 and January 2017 with their age range between 20 and 35 years. Twenty patients of them had been prepared for KTx. Fifty healthy women with regular menstrual cycles for at least 2 years and without fertility disorders coming to gynecology and obstetrics unit of the same hospital for regular checkup were selected as controls.

Exclusion criteria included patients with pregnancy, history of ovarian operation, severe illness, use of hormonal replacement therapy, or oral contraception. Women with BMI more than 30 kg/m^2, smokers, and patients with polycystic ovary syndrome were also excluded.

Patients and controls were subjected to thorough medical evaluation with detailed medical history (including menstrual regularity, age of onset of menstruation, number of pregnancies). In patient with ESKD, duration of CKD, onset of starting dialysis, and medication history were recorded. Biochemical tests were done including complete blood count, serum creatinine, uric acid, calcium, and phosphorus. Hormonal tests were done including follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and AMH. FSH and LH were done on third day of cycle if the patient had no amenorrhea. AMH level was measured in the beginning of the study in all patients and controls with repeated measures at 1 month, 6 months, and 12 months after transplantation in patients who received KTx. AFC was measured by ultrasound in all patients and control at the beginning of the study and it was repeated in the transplant group 12 months after KTx. Serum concentrations of FSH, LH, PRL, and AMH were assessed using a colorimetric enzyme-linked immunosorbent assay (Monobind, Inc., California, United States).

The participants were recruited from tertiary care hospital after approval of the institutional ethical committee. All patients provided informed consent to participate in this study. The study protocol and procedures conform to the ethical guidelines of the 1975 declaration of Helsinki.

Measurement of total AFC by ultrasound

Ovarian follicles are frequently counted using real-time 2D ultrasound. In day 2 or 3 of cycle of each patient, the patient was asked to empty her bladder, and then positioned in the lithotomy position. Scanning of the ovary was done using the transvaginal probe (Samsung Medison Sonoacer7 device) in both longitudinal plan and coronal plan, in order to identify which will offer the better image. After that, the ovary was centered on the screen and the US machine was adjusted to optimize image quality, in order to maximize the contrast between the follicular fluid and the ovarian stroma (including adjustments of gain, depth, and zooming in). Along the ovary largest axis, it should occupy at least 50% of the screen. All follicular structures ranged between 2 and 10 mm in diameter identified and it was scanned from one ovarian margin to the other. Any doubts whether a follicle lied within the 2–10 mm range, follicular size was measured using the internal diameter of the sonolucent area. For round follicles, only one measurement was required, however, for oval follicles, the mean of two diameters was calculated using the greatest diameter and the other greatest diameter perpendicular to it. Follicles out of mentioned range were subtracted from the total number of the identified follicles. If there was any doubt about the count, the process was repeated in the other scanning plane. After that the process was performed on the other ovary and reported separately [17].

Statistical analyses

Pre-coded data were entered and analyzed through the Statistical Package of Social Science Software program, version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Data were presented using mean, standard deviation, median and interquartile range for quantitative variables, and frequency and percentage for qualitative ones. Comparisons between groups were done using analysis of variance with multiple comparisons post hoc test in normally distributed quantitative variables while non-parametric Kruskal–Wallis test was used for non-normally distributed quantitative variables and Chi-square and Fisher's exact test for qualitative ones. A change in AFC and AMH was assessed through Wilcoxon test. p values < 0.05 were considered statistically significant.

Results

Baseline clinical, laboratory, and total AFC of women with ESKD compared to control subjects

A total of 60 females with diagnosis of ESKD for a mean duration of (6.6 ± 3.5 years) were enrolled in the study. They were treated with hemodialysis three times per week for (26.9 ± 8.8 months). Their mean age was (30 ± 3.9 years) and their menses started at mean age of (12.6 ± 1.6 years) which were not significantly different from that of the control group. Thirty-three patients with CKD had regular menstrual cycles and 14 women of them had got pregnancy. Mean AFC and AMH levels in patients with ESKD were significantly lower than those of the controls ($p < 0.001$). Furthermore, mean FSH, LH, and PRL levels were significantly higher in ESKD patients than control group ($p < 0.001$) (Table 1).

Table 1 Baseline clinical, laboratory, and ultrasonographic data of different groups

Variable	Hemodialysis group (n=60)	Transplant sub-group (n=20)	Control group (n=50)	*p value	**p value
Age (years)	30 ± 3.9	31.5 ± 4.1	29.6 ± 3	0.465	0.090
BMI (kg/m^2)	22.9 ± 1.8	23.2 ± 2	23.5 ± 1.5	0.069	0.596
Age of first menses (years)	12.6 ± 1.6	13 ± 1.7	12.9 ± 1.4	0.350	0.979
Cause of CKD no. (%)					
Diabetic nephropathy	20 (33.3)	7 (35)			
Hypertensive nephropathy	13 (21.7)	4 (20)			
Chronic GN	10 (16.7)	3 (15)			
Lupus nephritis	10 (16.7)	3 (15)			
Polycystic kidney	3 (5)	2 (10)			
TMA	3 (5)	0 (0)			
Congenital malformations	1 (1.7)	1 (5)			
Cycle regularity no (%)					
Regular	33 (55)	12 (60)	50 (100)		
Irregular	27 (45)	8 (40)	0 (0)		
Pregnancy after CKD no					
Yes	19	7			
NO	41	13			
AMH (ng/ml)	1.8 ± 1.2	1.7 ± 1.3	3.5 ± 1.7	<0.001	<0.001
FSH (IU/ml)	8.7 ± 1.6	8.8 ± 1.7	6.4 ± 1.1	<0.001	<0.001
LH (IU/L)	9.3 ± 3.3	8.9 ± 3.3	5.8 ± 1.1	<0.001	<0.001
Prolactin (ng/ml)	21.6 ± 4.4	20.5 ± 4.7	18.8 ± 2.5	<0.001	0.222
Total AFC	12 ± 4.6	11.1 ± 4.5	17.4 ± 4.3	<0.001	<0.001

Data are presented as n (%), mean $\pm$ SE

BMI body mass index, *CKD* chronic kidney disease, *GN* glomerulonephritis, *TMA* thrombotic micro-angiopathy, *AMH* antimüllerian hormone, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *AFC* antral follicle count

*p value: hemodialysis group versus control group

**p value: transplant group versus control group

Comparison between women with ESKD with regular menstrual cycles and those with irregular cycles

Women with ESKD and menstrual irregularity were not significantly different from those with regular cycles regarding mean age ($p = 0.946$), BMI ($p = 0.929$), age of onset of menses ($p = 0.186$), AFC ($p = 0.191$), or AMH level ($p = 0.368$). However, LH and PRL levels were significantly higher in women with menstrual irregularity than those with regular cycles ($p = 0.001$, $p = 0.034$), respectively (Table 2). Furthermore, none of patient who had menstrual irregularities before KTx had regular cycles after transplantation.

Baseline clinical, laboratory, and AFC of transplant patients compared to controls

The subgroup of ESKD patients who underwent successful KTx were 20 females. There was no statistically significant difference between renal transplant recipients and healthy women regarding mean age ($p = 0.090$) or age of onset of menses ($p = 0.979$). They had ESKD for (7.5 ± 3.8 years). The most common cause of renal disease in this group was diabetic nephropathy (35%). Menstrual cycles were regular in 12 patients of them and seven women gave birth after development of CKD at early stage of CKD (Table 1). After KTx, all of them received steroids and mycophenolate mofetil (MMF) which is associated increased risk of malformations and first-trimester pregnancy loss so, all patients avoided pregnancy during treatment with MMF. In addition, 13 patients received cyclosporine and seven patients received tacrolimus.

Creatinine, AMH level, and total AFC before and after renal transplantation

Mean creatinine before transplant was 8.2 ± 1.9 mg/dl (5.2–11.6 mg/dl), at 6 months after transplantation was 1.3 ± 0.3 mg/dl (0.8–1.9 mg/dl), and at 1 year after transplantation was 1.2 ± 0.3 mg/dl (1–1.9 mg/dl). Mean AMH level in transplant group was (1.7 ± 1.3 ng/ml) before KTx. AMH level showed significant stepwise reduction (1.5 ± 1.2 ng/ml at 1 month, 1.1 ± 0.9 ng/ml at 6 months and 0.9 ± 0.8 ng/ml at 1 year) after KTx (Fig. 1). Total AFC at 1 year after KTx was significantly lower than its value before KTx (6.6 ± 3.4 vs. 11.1 ± 4.5; $p < 0.001$) (Fig. 2).

We stratified transplant patient according to their age, AMH level showed significant reduction at 1 month ($p = 0.018$), 6 months ($p = 0.018$), and 1 year ($p = 0.018$) after KTx compared to AMH level before KTx. Same changes were observed with AFC (Table 3).

Discussion

Women with ESKD commonly have subnormal fertility which is related to the presence of menstrual cycle irregularities, sexual dysfunction, and hormonal abnormalities [18, 19]. Similar to previous study, our results showed that 45% of patients with ESKD had menstrual irregularities [19]. Oligo-ovulation or anovulation is the major factor for these menstrual cycle abnormalities in uremic women [20]. This ovarian dysfunction could be related to hypothalamic pituitary–gonadal dysfunction found in uremic patients as a result of hyperprolactinemia due to increased secretion or deceased clearance of prolactin [20]. Serum prolactin

Table 2 comparison of baseline characteristics hemodialysis women with and without menstrual irregularities

| Variable	Control group n = 50	Hemodialysis women with irregular menstrual cycles n = 27	Hemodialysis women with regular menstrual cycles n = 33	* p value
Age (years)	29.6 ± 3	29.9 ± 4.5	30.1 ± 3.4	0.946
BMI (kg/m^2)	23.5 ± 1.5	22.9 ± 1.9	22.9 ± 1.6	0.929
Age of first menses (years)	12.9 ± 1.4	12.4 ± 1.7	12.8 ± 1.6	0.186
Duration of CKD (years)	–	7.7 ± 3.6	5.6 ± 3.1	**0.029**
Period of Hemodialysis (months)	–	27.1 ± 9.1	26.7 ± 8.6	0.853
AMH (ng/ml)	3.5 ± 1.7	1.7 ± 1.3	1.9 ± 1.1	0.368
FSH (IU/ml)	6.4 ± 1.1	8.8 ± 1.8	8.5 ± 1.4	0.364
LH (IU/ml)	5.8 ± 1.1	10.9 ± 3.4	8 ± 2.6	**0.001**
Prolactin (ng/ml)	18.8 ± 2.5	23 ± 4.5	20.4 ± 4.1	**0.034**
Total AFC	17.4 ± 4.3	11 ± 4.1	12.7 ± 5	0.191

Data are presented as n (%), mean ± SE

BMI body mass index, *CKD* chronic kidney disease, *AMH* antimüllerian hormone, *FSH* follicle stimulating hormone, *LH* luteinizing hormone, *AFC* antral follicle count

*p value bold indicates the statistically significant values between hemodialysis women with regular and irregular cycles with $p < 0.05$
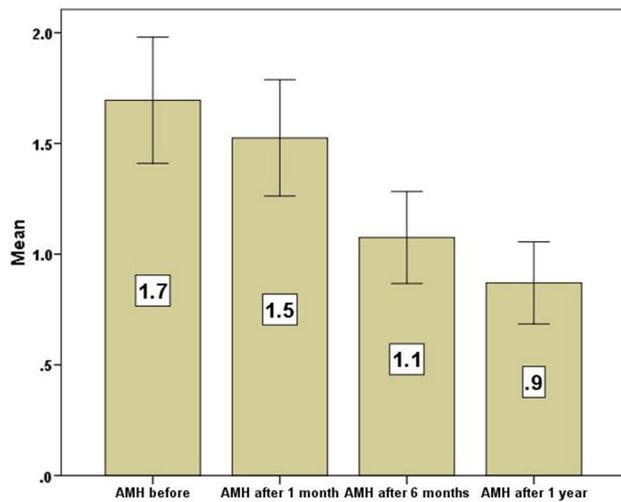
Fig. 1 Serum AMH levels before and after renal transplantation in women with CKD. Mean AMH level was significantly lower at 1 month (1.5±1.2 ng/ml), 6 months (1.1±0.9 ng/ml), and 1 year (0.9±0.8 ng/ml) following KTx compared to its level before KTx (1.7±1.3 ng/ml). Taking base line AMH level as reference the mean difference was (−0.17 ng/ml) at 1 month, (−0.62 ng/ml) at 6 months,(−0.83 ng/ml) at 1 year after KTx with *p value* < 0.001;<0.001; <0.001, respectively, using Wilcoxon test
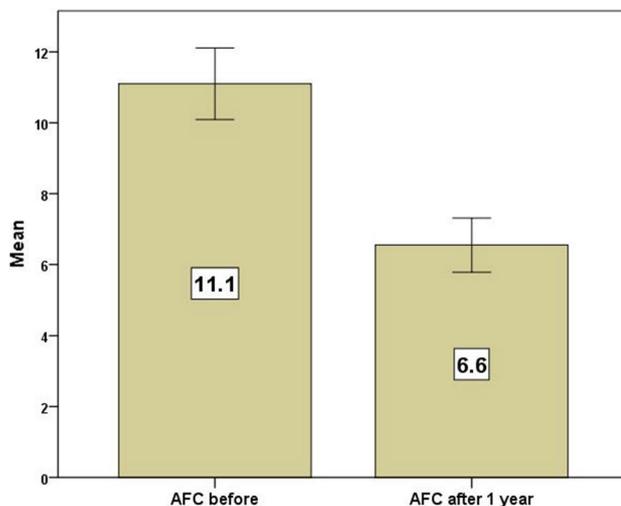
Fig. 2 Total AFC before and 1 year after KTx. AFC was significantly reduced after KTx (6.6±3.4) compared to AFC before Ktx (11.1±4.5). Using Wilcoxon test the mean difference was (−4.6; 95% CI: −5.7 to −3.4) (*P<0.001*)

level rise correlates with decline in glomerular filtration rate. Increase in serum prolactin levels is mainly due to decreased dopaminergic inhibition of prolactin release from pituitary gland in addition to decreased LHRH release. Prolactin is considered as a toxin causing infertility in uremic patient. It can cause menstrual abnormalities (amenorrhea

and oligomenorrhea) and galactorrhea in CKD females [20, 21]. This goes with our results that patients with ESKD had higher levels of LH, FSH, and PRL than age-matched healthy subjects. Furthermore, women with ESKD who experienced menstrual irregularities had higher levels of LH and PRL compared to those with regular cycles.

In previous study in the general population, longer and more irregular menstrual cycles were found in women with elevated AMH concentrations [22]. In addition, studies attempted to assess AMH level in CKD women receiving hemodialysis revealed low level of AMH in these patients compared to healthy population [7, 12]. In the current study, AMH level was lower in patients with ESKD compared to age-matched healthy women. However, we did not find significant difference of AMH level between ESKD women with menstrual irregularities and those with regular cycles. This might suggest a decrease of AMH secretion by the damaged granulosa cells and a reduction of ovarian reserve in ESKD patients irrespective to the presence of menstrual irregularities [7]. In support of this assumption, patients with CKD were found in previous study to undergo menopause 4.5 years earlier compared to general population which is suggestive of alternations in ovarian reserve in this group [21]. Moreover, we reported for the first time that patients with ESKD have decreased ovarian reserve as indicated by lower total AFC compared to age-matched healthy women.

Although successful, KTx improves the severity of many hormonal disturbances, fertility is still lower in women who undergo transplantation than fertility in healthy females [23]. Renal transplantation can abolish hormonal abnormalities found in patients with CKD, resulting in more ovulatory cycles and regular menstruation [24, 25]. Previous studies reported that transplant recipients had four times higher pregnancy rate than hemodialysis women and 2–5% of them experienced pregnancies after successful KTx [26, 27]. Yet, successful pregnancy in transplant recipients occurs 10 times less than in the general population which could be related to alterations of ovarian function [7]. In support of this hypothesis, our study revealed a significant reduction of AMH level and total AFC after successful KTx. Decline of serum AMH after renal transplant has been reported by two previous studies; however, there is no previous data about AFC after KTx [7, 12]. The reason for this decline in serum AMH is not clear. AMH might decrease after KTx due to improved renal excretion [7]. However, the reduction of AFC after renal transplantation points to significant fall in ovarian reserve in transplant recipients. This finding could be related to firstly, the deleterious effect of the original disease on fertility that one-third of our patients had diabetes and one-third had glomerulonephritis and systemic lupus which are commonly associated with reproductive abnormalities and premature menopause [28, 29]. Secondly, the toxic effect of immunosuppressive drugs on gonads, our patients received

Table 3 Changes of AFC and AMH levels by time with age stratification

Age	Variable	Mean ± SD	Mean differences	95% CI	*P* value
≤ 30 (n = 7)	AFC before KTx	16.7 ± 1.5	**Reference**	**Reference**	**Reference**
	AFC after 1 year	10.1 ± 2.6	− 6.57	(− 9.12 to − 4.02)	**0.017**
	AMH before KTx	3.1 ± 1.1	**Reference**	**Reference**	**Reference**
	AMH after 1 month	2.7 ± 1.1	− 0.31	(− 0.44 to − 0.19)	**0.018**
	AMH after 6 month	2.1 ± 0.8	− 0.99	(− 1.44 to − 0.53)	**0.018**
	AMH after 1 year	1.7 ± 0.8	− 1.34	(− 1.76 to − 0.93)	**0.018**
> 30 (n = 13)	AFC before KTx	8.1 ± 1.7	**Reference**	**Reference**	**Reference**
	AFC after 1 year	4.6 ± 1.8	− 3.46	(− 4.34 to − 2.59)	**0.001**
	AMH before KTx	1 ± 0.5	**Reference**	**Reference**	**Reference**
	AMH after 1 month	0.9 ± 0.5	− 0.09	(− 0.16 to − 0.03)	**0.013**
	AMH after 6 month	0.5 ± 0.4	− 0.42	(− 0.55 to − 0.3)	**0.001**
	AMH after 1 year	0.4 ± 0.3	− 0.55	(− 0.69 to − 0.4)	**0.001**

Data are presented as n (%), mean ± SE

AMH antimüllerian hormone, *AFC* antral follicle count, *KTx* kidney transplantation

Bold indicates the statistically significant values with $p < 0.05$

steroids, mycophenolate mofetil, cyclosporine, and tacrolimus which are associated with a low risk of adverse effects on fertility [30]. Thirdly, the age of the patient could affect the ovarian reserve, however, this decline in AMH and AFC was observed in ESKD patients of different age groups.

Increased fertility after renal transplantation has been reported by previous studies [6, 24]. Although, we did not investigate the occurrence of pregnancy in post-transplant period because the duration of the study was only 1 year, there was significant reduction in AFC and AMH in our study. This discrepancy could be explained by the fact that ovarian reserve is not the only factor affecting the fertility in KTx patients and improvement of hormonal disturbances which has been noted after KTx in previous studies could be an important player in the occurrence of successful pregnancy [6, 24].

Limitations of this study should be mentioned first, the modest number of enrolled patients. Second, large proportion of young women had ESKD secondary to diabetic nephropathy which may limit the generalizability of this study. Third, AMH was performed in the control group once because of logistic obstacles.

Conclusion

In conclusion, hemodialysis women with CKD have significantly lower AMH level and total AFC than age-matched healthy controls. Moreover, significant reduction of serum AMH and total AFC was found after successful renal transplantation which indicates reduction of ovarian reserve in patients with CKD that even decline after KTx. Cryopreservation for the ova could be considered for those patients in further studies, and this technique may be used to preserve their fertility potentiality. So, further experimental studies may be needed to prove this hypothesis.

Compliance with ethical standards

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