

Pre-Mature Ovarian Failure and its Association with Perceived Stress After Chronic Kidney Disease Diagnosis: A Challenge in all CKD Stages

Sana Tariq¹, Lubna Razzak², Sehrish Rasool³, Najia Bhatti⁴

¹Manager, Research and Development, Tabba Kidney Institute, Karachi

²Consultant Urogyneacologist, Urology Department, Tabba Kidney Institute, Karachi

³Senior Registrar Obs & Gynae, Pir Abdul Qadir Shah Jeelani Institute of Medical Sciences Gambat khairpur Mir

⁴Assistant Professor Obs & Gynae, Shaheed Muhtarma Benazir Bhutto medical university, Larkana

Correspondence: Dr. Sana Tariq

Manager, Research and Development, Tabba Kidney Institute, Karachi.

sanatariqrajput@gmail.com

Abstract

Objective: To assess the frequency of pre-mature ovarian failure in chronic kidney disease stage and its association with perceived stress.

Methodology: This was a prospective, cross-sectional, observational study that will take place at the Tabba Kidney Institute's Nephrology Department in Karachi from April 2021 to October 2021. Pre structured questionnaire was used to get all necessary information regarding demographics, menstrual history before and after chronic kidney disease, pregnancy outcomes and purposive, no probability sampling technique was used. FSH levels were checked in premenopausal females to diagnose Premature Ovarian failure, described as > 40 IU/L FSH levels within 40 years of age. SPSS was used to analyze the data.

Results: There were a total of 182 participants FSH results were > 40 IU/L with a mean value of 86.2 ± 27.8 IU/L. Hematological parameters indicated noticeably decline of serum creatinine results in patients without POF symptoms. Hemoglobin and other investigations, including serum urea, albumin, and platelets were almost similar in both groups.

Conclusion: Incidences of menstrual disturbances, premature ovarian failure and perceived stress is excessively reported in patients with chronic kidney disease stage III, IV and end stage renal disease. Psychological consultation is required on a regular basis for all patients in order to maintain better mental health, understand coping mechanisms, and accept the disease prognosis.

Keywords: Pre-mature ovarian failure, chronic kidney disease, conception after CKD

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Introduction

Chronic kidney disease is an emerging public health problem in Pakistan with asymptomatic population suffering undiagnosed and untreated in urban and rural areas, the management of chronic diseases is already compromised while chronic kidney disease management has been neglected from years. In females the pattern of disease, progression, and management should be different. Along with other gender based factors such as risk of cardiovascular issues, urinary tract infections, hormonal imbalance, fertility issues are the most neglected factors in chronic kidney disease patients. Getting pregnant with chronic kidney disease is challenging because, as the disease progress the sexual function and fertility declines, with

increased risk of adverse pregnancy outcomes and severe complications such as miscarriages, preeclampsia, premature birth etc.^{1,2} The day to day management of chronic kidney disease factors, fluid restrictions, dietary restrictions, medications and hormonal imbalance increases the chances of perceived stress.³ On other hands menstrual disturbances, anovulatory cycle, irregular menstrual cycle resulting infertility is a known factor of triggering stress and depression in females. Marital satisfaction and sexual dysfunction are the results of reproduction related stress and depression.⁴ A chronic kidney disease diagnosis is a shock for females in the fertile window age group (15-49 years), which is associated with menstrual

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irregularities and premature menopause caused by premature ovarian failure, making this group vulnerable. While many studies have been conducted to assess the value of referring CKD patients to gynaecologists from nephrologists,⁵ The analysed determinants of chronic kidney disease in the Pakistani population are age, hypertension, increased fasting blood glucose, stroke, and raised cholesterol levels.⁶ Gynecological problems are highly reported in chronic kidney disease patients, along with irregular menstrual cycle, polymenorrhea, oligomenorrhea, amenorrhea and pre mature menopause. Approximately two-third of the total chronic kidney disease patients have menstrual issues, with 50-100% prevalence of amenorrhea in end stage renal disease, who start menstruating while of dialysis.⁷⁻⁹

Pregnancy in any stage of Chronic Kidney Disease increases the risk of adverse outcomes by five fold as compared to normal population. The most important and dangerous adverse maternal outcome is progression in renal failure, which is the key reason of nephrologists to avoid pregnancy and counsel for contraception.¹⁰⁻¹³

The term Pre-mature ovarian failure used for amenorrhea as a result of complete cessation of ovarian function before natural menopause age, the associated symptoms of pre-mature ovarian failure are primary or secondary amenorrhea, hypoestrogenism, sexual hormonal deficiency, and infertility. Diagnosis of POF has been defined since the early 1950s specifying secondary loss of menses, hot flashes, infertility, endometrial atrophy and elevated follicle stimulating hormones (FSH) levels before 40 years of age.¹⁴⁻¹⁷ The age categories for the incidences of pre-mature ovarian failure are distributed in 20, 30 and 40 years of age with the prevalence rates of 1/10,000, 1/1000 and 1/100 respectively.^{16,18,19} Many autoimmune disorders, immunosuppressive treatments, chronic illnesses such as diabetes or chronic kidney disease, iatrogenic causes such as chemotherapy, radiation, and surgery, some infections can also trigger early menopause, Turner syndrome, and a few studies have shown the idiopathic causes as well.²⁰⁻²² Chronic kidney disease triggers pre mature ovarian failure almost immediately with the onset of stage III to End stage renal disease. The prevalence of chronic kidney disease has been on upsurge from past few decades, Asian countries have encountered the incidences in child bearing aged females, and pre-mature ovarian failure is one of the prime reproductive concerns in our chronic kidney disease population, as the social norms are strictly followed in many areas in order to use contraception. The inability to conceive and

reproduce can lead to a stressed marital relationship and, in many cases even divorce. The association of stress with early menopause has been evaluated in many races from many researchers, the results showed the increase in the risk of stress and depression in females experiencing early menopause.^{3,21,23-25} A study from interior Sindh, Pakistan, measured the risk of early menopause in chronic disease patients, including those with diabetes, cardiac issues and psychiatric illness as well.²⁶ The perceived stress scale has been used to assess the perception of daily life unpleasant events and the perception of participant regarding these events in many studies. Chronic kidney disease patients are known to be on high risk for stress.²⁷⁻²⁹ Although the chronic kidney disease influence was not assessed. The aim of this study is to assess the frequency of premature ovarian failure in reproductive aged females diagnosed with different stages of chronic kidney disease, and its impact on psychological health, social, and marital life.

Methodology

This is a prospective, cross-sectional, observational study that will take place at the Tabba Kidney Institute in Karachi from April 2021 to October 2021. The patients were enrolled in the study after explaining the research and obtained their informed consent. A pre structured questionnaire was used to get all necessary information regarding demographics, menstrual history before and after chronic kidney disease, pregnancy outcomes, and indication of stress that was measured, patients indicating cessation of menstrual cycle before the age of 40 years were asked to give blood sample for follicular stimulating hormones estimation and confirming the diagnosis of premature ovarian failure.³⁰ Purposive, no probability sampling technique was used for sampling. Ethical approval was taken from Institutional ethical review committee. The inclusion criteria was fertility Age Range 15-49 years and surgical menopause related to menstrual disorders. While coagulation disorder, surgical menopause not related to menstrual disorders and thyroid disorders were excluded. The total number of childbearing female Pakistani population in 2020 with constant fertility is 107220.324; according to UN data the website had age distribution data too. After putting this value in 3 different sample size calculators, Sample size was calculated using Rao soft sample size calculator the obtained sample size was 384, where confidence level was 95% and Margin of error was 05%.

This technique will be purposive, non-probability sampling, detailed medical history, including age of menarche, menstrual cycles regularity, oligomenorrhea

or sudden amenorrhea were differentiated. Secondary loss of menses, hot flushes, excessive sweating, hair loss, as well as skin and mucous membrane dryness taken from patients for accurate diagnosis of premature ovarian failure with the help of gynecologist.

The descriptive statistical tests were performed for dependent variables. The measure of association was analyzed with the help of Paired sample T Test, and a compare means test, and for the validity of data, a chi-square test was performed. P-Value of < 0.05 was considered significant.

Results

The mean age of participated subjects was 41.31 ± 7.7 , with minimum 26 years of age and maximum 49 years. Hypertension is the most common co morbidity of chronic kidney disease, with 168 (43.8%) of 384 patients. Follicular stimulating hormones test was performed to confirm the FSH levels, results >40 IU/l were mentioned as premature ovarian failure as per the referenced studies. Total 182 participants FSH results were > 40 IU/L with mean value of 86.2 ± 27.8 IU/L. Demographic details were categorized with premature ovarian failure diagnosis, specified 174 (45.3%) of 384 married participants with premature ovarian failure. Hematological parameters indicated noticeably decline of serum creatinine results in patients without POF symptoms. Hemoglobin and other investigations including serum urea, albumin, and platelets, were almost similar in both groups. (Table I)

The pre-mature ovarian failure was described as menopause within the age of 40 years. Table II indicated the measure of association of menopause after chronic kidney disease diagnosis into all CKD stage from Stage I to stage IV and End stage renal disease. The results showed almost equal number of study subjects indicating premature ovarian failure (menopause before the age of 40 years), with 19% (73/384) in CKD stage IV and 21.3% (82/384) In ESRD. Chronic kidney disease stage I and II patients reported successful conception with 33 (8.5%) and 18 (4.6%) of the 18 frequencies, respectively.

The frequency of premature ovarian failure was specified in study participants with frequency of 182 (47.3%). POF has been diagnosed after CKD stage II and its prevalence is reported highest in stage III and IV. While menopause, (Cessation of menstrual cycle) was reported in 188 (48.3%) of 384 participants. (Figure 01)

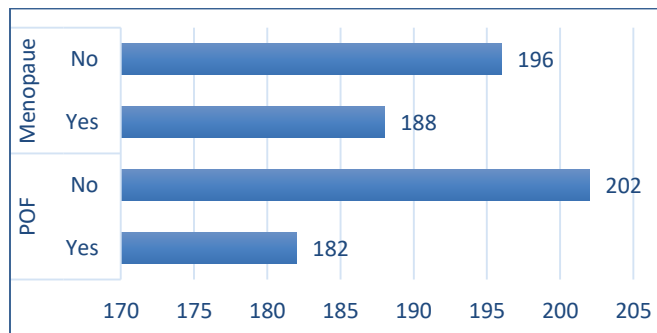


Figure 1. Pre Mature ovarian failure and menopause frequency in study participants.

Table I: Demographic details of study participants.

Variable	Premature Ovarian Failure		P value
	Yes	No	
Age	38.9 ± 6.6	44 ± 5.7	< 0.005
Parity	3.7 ± 1.9	3.0 ± 2.0	0.2
Follicular stimulating Hormone (FSH)	86.2 ± 27.8	16.8 ± 9.2	< 0.005
Marital Status	Married	174 (45.3%)	0.1
	Unmarried	8 (2%)	
Education	None	17 (4.4%)	<0.05
	Middle	57 (14.8%)	
	Matriculation	25 (6.5%)	
	Intermediate	64 (16.6%)	
	Graduation	19 (4.9%)	
Laboratory investigations	Post-graduate	0	0.5
	Urea	90.9 ± 42.4	
	Creatinine	6.4 ± 3.3	
	Hemoglobin	11.0 ± 1.9	
	Albumin	3.6 ± 0.9	
Platelets	195.0 ± 93.9	190.1 ± 83.6	0.5

Table II: Measure of association of CKD stage with Menstrual disorder & Stress in CKD patients:(n=384)

Variables:	CKD I	CKD II	CKD III	CKD IV	ESRD	P value
Menopause	0	9	24	73	82	< 0.05
Conceived After CKD	33	18	0	0	0	< 0.05

The perceived stress scale specified the calculation of results indicating stress levels of participants within the low, moderate, and severe categories. The mild form of perceived stress is low category with chances of managing stress is higher, moderate category indicates slight danger of participant with more complicated behavior and hopelessness of participant. While high stress category indicates the most vulnerable and dangerous situation requiring interventions immediately.

Participants with known premature ovarian failure were fall into all three categories indicated above, 21(5.4%) of 384 participants showed low stress levels, while 115 (29.9%) showed moderate levels of stress and only 46(11.9%) were reported as High risk for perceived stress and required immediate intervention.

Discussion

The onset of pre-mature ovarian failure right after the diagnosis or progression of chronic kidney disease has been previously reported.^{19,31} Other menstrual irregularities, including polymenorrhea, oligomenorrhea and secondary amenorrhea were reported in chronic kidney disease stage III, IV and end stage renal disease specifically, while early stage like stage I and II have very low incident rates^{32, 33} These results explain the conception outcomes and sustainable pregnancy, as only 51 out of 384 participants had a history of successful conception and delivery without any foetal or maternal adverse outcomes in our study, however, all the pregnant females were diagnosed with Stage I and II CKD. The hormonal changes are more prone in child bearing ages, the menstrual irregularities and infertility are individual determinants of stress and been evaluated in many studies.⁸ Many studies indicated the difference of gender in coping strategies and stress vulnerability.³⁴

The systematic declining of reproductive physiology in females with progression of chronic kidney disease has not been studied completely, nephrologists consider it an adverse reaction of renal malfunction, which may be correct as renal function impairment cause hormonal disturbance.³⁵⁻³⁷ the wish of getting pregnant and social pressure as well as peer pressure tends to create stressful environment for chronic kidney disease patients. The nephrologists are usually hesitant to agree on the patient's pregnancy, but prompt them to go for contraceptives in order to minimize the risk of pregnancy and exclude the adverse effects of pregnancy on disease progression. The counselling of nephrologists are more important than assumed in order to enable patients and their spouse importance of the decision and

describing actual outcomes.⁴ Perceived stress scale results indicated a higher frequency of moderate stress participants, although high risk category prevalence is not decreased as well, the need of psychological interventions, awareness, understanding of coping mechanisms, and other psychiatric help is required for females CKD patients in order to maintain their quality of life and psychological wellbeing.

Conclusion

Incidents of premature ovarian failure has positive association with chronic kidney disease progression and results in higher perceived stress in patients. Conservative management to preserve ovarian function in early stages of CKD are recommended, and psychological consultation is a necessity for understanding of coping mechanism and accepting the disease prognosis.

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