International Journal of Drug Research and Technology

Available online at http://www.ijdrt.com

Research Article

STUDY OF GONADAL HORMONES IN EGYPTIAN FEMALE CHILDREN WITH END STAGE RENAL DISEASE UNDER REGULAR HAEMODIALYSIS IN CORRELATION WITH DIALYSIS DURATION

Mohamed A El-Gamasy[*], Mohamed M Abdelmageed and Mohammed Abd Ellatif Nassar

Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta, Gharbia Governate, Egypt

ABSTRACT

Background: Estradiol hormone is susceptible to significant pathophysiological alterations in children with End Stage Renal Disease (ESRD) under regular hemodialysis (HD), leading to delayed pubertal maturation. Aim of the work was to evaluate the plasma levels of follicular stimulating hormone (FSH), luteinizing hormone (LH) and estradiol hormone in female children and adolescents with ESRD under HD and its correlation with dialysis duration.

Subjects and Methods: This study was carried out on 40 girls with ESRD under regular HD who were attending the Pediatric Nephrology Unit of Tanta University Hospital at Egypt.Forty age- and sex-matched children were served as controls. Puberty was assessed according to Tanner's classification with measurements of serum FSH, LH to assess hypothalamic pituitary gonadal axis and serum estradiol levels.

Results: There were significantly lower FSH, LH, and estrogen levels in Group I compared with Group II. Mean FSH level was 1.36 ± 0.22 mIU/mL in Group I *vs.* 2.64 ± 0.81 mIU/mL in Group II with. Mean LH level was 0.11 ± 0.006 mIU/mL in Group I *vs.* 1.78 ± 1.12

mIU/mL in Group II. Mean estrogen level was 26.69 ± 21.59 pg/mL in Group I *vs*. 51.03 ± 26.50 pg/mL in Group II.There was significant negative correlations between the dialysis duration and serum FSH,LH and Estradiol levels in patients group.

Conclusions: Female patients with ESRD had delayed puberty secondary to gonadal hormones deficiency including FSH, LH, estrogen with significant negative correlations between them and duration of hemodialysis.

Keywords: Follicular Stimulating, Lutenizing, Hormone, Estradiol, Renal, Hemodialysis, Children.

BACKGROUND

The sex hormones are susceptible to pathophysiological alterations in chronic renal failure (CRF), which may lead to delayed or arrested pubertal maturation (Gupta, *et al*., 2012). These endocrine disorders result in growth failure and increase the difficulties of transition from childhood to adulthood (Dötsch, *et al*., 2004) and thus sexual dysfunction is followed (Chan, *et al*., 2002). Pubertal delay was reported in more than half of the girls and one third of boys with ESRD. Variable mechanisms were attributed to delayed puberty in these children including neuroendocrine impairment in the pituitary gonadal axis, peripheral alterations due to uremia (Giusti, *et al*., 1993)**,** gonadal damage and impaired regulation of gonadotropin secretion (Armanini, *et al*., 2004). The aim of the work was to evaluate the plasma level of FSH, LH and Estradiol hormones in children and adolescents with ESRD under regular HD and its correlation with dialysis duration.

SUBJECTS AND METHODS

This study was carried out upon 40 female children and adolescents with ESRD under regular HD. Their ages ranged from 10-18 years with a mean value of 14.63 + 2.66 years who were attending the Pediatric Nephrology Unit of Pediatric Department of Tanta University Hospital in the period from August 2016 to August 2017. Forty, age matched female children were chosen and served as controls. The study was conducted after approval from the

esearch Ethical Committee of the Faculty of Medicine, Tanta University and informed written or verbal consents from parents of included girls.

All patients were on regular HD, Dialysis was started when GFR is equal or less than 15 ml/min/1.73m^2,three times per week, with each dialysis session lasting from three to four hours. Patients were dialyzed on Fresenius 4008- B dialysis machine (Made in Germany) at blood flow rate = 2.5 x weight (kg) + 100ml/min., using polysulphane hollow fiber dialyzers which were suitable for the surface area of the patients (Fresenius F3 = 0.4 m^2, F4 = 0.7m^2, F5 = 1.0m^2 and F6 = 1.2m^2). Bicarbonate dialysis solutions were used. All patients were receiving supportive therapies in the form of subcutaneous erythropoietin in a dose of 50 IU/Kg/session, IV iron dextran in a dose of 100 mg/Kg/week, oral folic acid in a dose of 1 mg/day, oral calcium in a dose of 1000 mg/day, oral vitamin D (one alpha) in a dose of 0.01-0.05 µg/Kg/ day and oral antihypertensive medications for only hypertensive patients. In our study Magnesium therapy (which considered as a supportive therapy also) was given for selected cases who had increased levels of serum phosphous levels and or had increased levels of serum PTH above normal for age.

Inclusion criteria

All female children and adolescents with ESRD treated by regular maintenance.

Exclusion criteria

Patients of primary endocrinal diseases, under hormonal therapy, using drugs known to affect Estradiol hormone levels, or adolescent girls who already get full puberty before onset of ESRD.

ALL PATIENTS AND CONTROLS WERE SUBJECTED TO

Full History Taking

It includes age, history of hypothyroidism, type 1 diabetes mellitus, or zinc deficiency. Child's previous growth and development, the precise timing and sequence of the physical and behavior changes of puberty, timing of appearance of axillary and pubic hair, onset of menarche (the onset of menstruation).

Through clinical examination

Thorough clinical examination including anthropometric measurements for assessment of nutritional and developmental status which included weight which was recorded with minimal clothing using electronic weight scale in Kilograms, *Height:* by measuring the distance from the vertex to the base of the heel in centimeters by using a stadiometer in standing position, *Body mass index (BMI)* which was calculated by Formula: BMI= weight (kg)/[height (m)]^2 (Romero-Corral, *et al*., 2008)**.** *Mid Arm Circumference (MAC)* by measurement of the circumference of the left upper arm at the mid-point between the tip of the shoulder (olecranon process) and the tip of the elbow (the acromium process) in centimeters**,** *Vital signs* especially *arterial blood pressure* which was measured by auscultatory method using a mercury sphygmomanometer, in the semi setting position after 10 minutes of rest, in the non fistula arm using an appropriate sized cuff and was taken as the mean value of 3 successive readings in 3 different days and *Pubertal assessment* which measure rating of genital development and were assessed according to *Tanner's staging* (Tanner, *et al*., 1976 and Sun, *et al*., 2012), which assess *Pubic and axillary hairs, Breast development* by labeling bras with letter indicating the depth of the cups which cradle the breasts, Breast volume measurement by using graduated cylinder and elevation and areola is determined (Palin, *et al*., 1986).

Puberty is preceded by adrenarche (the early appearance of axillary and pubic hair) between ages 6–10 years, which can be transient and disappear before the onset of true puberty (Plant TM 2001)**.** On average, girls begin puberty at ages 10–11years and usually complete puberty by ages 15–17 years (Kail, *et al*., 2010). Onset of menarche for females between ages 12–13 years (Anderson, *et al*., 2003). Delayed puberty is defined as the absence of pubertal onset by the expected age or once puberty has commenced failure of appropriate progression (Garibaldi, 2004). Girls are considered to have delayed puberty if they reach the age of 12 years without evidence of pubertal changes (Eugster, et al., 2001).

Laboratory investigations

Laboratory investigation including complete Blood Count (CBC)which measured by an automated analyzer, Blood urea, Blood Urea Nitrogen (BUN), serum creatinine, serum

albumin and serum electrolytes (ionized calcium, Potassium and Phosphorus),Serum FSH, LH and Estradiol levels.

Specimen Collection and Handling

Venous blood morning samples were withdrawn just before dialysis sessions. Five milliliters of venous blood were collected using sterile needles through gentle venipuncture after sterilization of the puncture site with alcohol, and collected samples were divided into 2 mL in 20 lL ethylenediaminetetraacetic acid (EDTA) solution for complete blood count including differential white blood cells count which was done on a Leishman stained peripheral blood smear with evaluation using an ERMA PCE-210 N cell counter (fully automated blood cells. counter from ERMA. Inc., Japan) (George-Gay, *et al*., 2003) and 3 mL in a plain tube that allowed for clotting in a water bath at 37 C. After clotting, centrifugation was done at 1500 g for 10 min. Separated serum was collected in a tube for assessment of FSH, LH, and estrogen serum levels. Samples were collected in puberty girls during the follicular phase of menstrual cycle (From the day 7 to the day 10 from last menstrual period to record the estrogen surge). Kit supplied by (TOSOH Bioscence) (Wide, 1981 and Gilbert-Barness, et al., 2003).

Statistical Methods

Statistical package for social science (SPSS) version 18.0 was used for analysis of data. Data was summarized as mean ± standard error of the mean (SE). Non-parametric test (Mann-Whitney) was used for analysis of 2 independent quantitative variables. Pearson's correlation was also done where the r value was considered weak if <0.25, mild if $\geq$ 0.25 - < 0.5, moderate if $\geq$ 0.5 -< 0.75 and strong if $\geq$ 0.75. P value was considered significant if $\leq$ 0.05 (Khothari, CR 2012).

RESULTS

Table 1 Summarized demographic data of the studied patients and control groups as regard age, anthropometric measurements, blood pressure and dialysis duration.

The age ranged from 10-18 years with mean 14.63 ± 2.66 in patients group and 14.25 ± 2.64 in control group. The mean values of anthropometric measurements including weight, height,

BMI and MAC of patients group was significantly lower than that of control group. Both systolic and diastolic blood pressures of the patients group were significantly higher in patients group than that in control group (P<0.05). Duration of dialysis in patients group ranged from 3 – 12.3 years with mean 7.2 ± 2.51 year.

Table 1: Demographic data of the studied patients and control groups.

		Patients	Controls	Statistical test	P. value
Age (years)	**Range**	10 – 18	10 – 18	t=0.200	0.657
	Mean ± SD	14.63 ± 2.66	14.25 ± 2.64		
Duration of dialysis (yearss)	**Range**	3 – 12.3	-	-	-
	Mean ± SD	7.2 ± 2.51			
Weight (kg)	**Range**	20 – 55	35 – 78	25.146	0.001*
	Mean ± SD	36.43 ± 10.51	54.85 ± 12.63		
Height (cm)	**Range**	102 – 162	141 – 180	14.561	0.001*
	Mean ± SD	137.75 ± 17.86	156.75 ± 11.03		
Body Mass Index(BMI) (Kg/m2)	**Range**	13.6 – 32.6	17 – 31	4.664	0.037*
	Mean ± SD	19.14 ± 4.68	21.91 ± 3.31		
Mid Arm Circumference (MAC)(cm)	**Range**	13 – 26	21 – 30	33.403	0.001*
	Mean ± SD	19.75 ± 3.71	25.55 ± 2.52		
Systolic blood pressure (mm Hg)	**Range**	120 – 160	100 – 130	17.366	0.001*
	Mean ± SD	139.25 ± 10.04	114.50 ± 7.59		
Diastolic blood pressure (mm Hg)	**Range**	80 – 110	60 – 80	20.829	0.001*
	Mean ± SD	95.5 ± 7.42	74 ± 5.98		

t = student t test; X2 Chi square test; P. Value < 0.05 significant

Table 2 showed that there were significant difference between studied groups as regarding Tanner staging with delayed puberty in ESRD group when compared with control group (P<0.05).

Table 2: Tanner's stage distribution between the patients and control groups.

Tanner's stage			Patients	Controls	Total
I		**N**	12	10	30
		%	30.00%	25.00%	37.50%
II		**N**	16	6	22
		%	40.00%	15.00%	27.50%
III		**N**	10	12	22
		%	25.00%	30.00%	27.50%
IV		**N**	2	9	11
		%	5.00%	22.50%	13.75%
V		**N**	0	3	3
		%	0%	7.50%	3.75%
Total		**N**	40	40	80
		%	100.00%	100.00%	100.00%
Chi-square test	X^2 value		4.456		
	P-value		0.033		

P. Value < 0.05 significant

Table 3 summarized routine laboratory data of the studied patients and control groups, there was significant increase in levels of blood urea, BUN, serum creatinine serum potassium and serum phosphorus levels in patients group when compared to control group. (P<0.05).But there was significant decrease in levels of hemoglobin percent, hematocrit values, platelet count, total leucocytic count, serum albumin and serum ionized calcium in patients group

Table 3: Routine investigations of the cases group and the control group.

		Patients	Controls	T. test	P. value
Blood Urea (mg/dl)	**Range**	100.8 – 257	21.7 – 36.7	53.71	0.001*
	Mean ± SD	168.33 ± 50.03	28.99 ± 4.84		
Serum Creatinine (mg/dl)	**Range**	4.9 – 10.3	0.5 – 1.4	87.35	0.001*
	Mean ± SD	7.76 ± 1.53	0.91 ± 0.27		
BUN (mg/dl)	**Range**	45 – 115	9.6 – 16.3	59.09	0.001*
	Mean ± SD	76.01 ± 22.30	12.81 ± 2.19		
HB (g/dl)	**Range**	7.2 – 12.4	11.2 – 13.9	46.31	0.001*
	Mean ± SD	10.45 ± 1.44	12.84 ± 0.74		
HCT %	**Range**	21.5 – 37.9	33.6 – 42	37.71	0.001*
	Mean ± SD	31.61 ± 4.48	38.37 ± 2.31		
PLT ×1000/cmm	**Range**	133 – 414	250 – 435	39.73	0.001*
	Mean ± SD	223.05 ± 81.65	357.90 ± 49.89		
WBC ×1000/cmm	**Range**	3.4 – 9.1	4.1 – 12.5	4.575	0.039*
	Mean ± SD	5.74 ± 1.77	7.05 ± 2.08		
Serum Albumin (g/dl)	**Range**	2.8 – 4.6	3.6 – 5.5	19.73	0.001*
	Mean ± SD	3.69 ± 0.54	4.52 ± 0.64		
Serum Ionized Ca (mg/dl)	**Range**	2.44 – 5.2	4.2 – 5.5	21.67	0.007*
	Mean ± SD	4.08 ± 0.69	4.89 ± 0.36		
Serum K (mmol/l)	**Range**	3.5 – 6.1	3.5 – 5.2	20.84	0.001*
	Mean ± SD	5.14 ± 0.74	4.22 ± 0.52		
Serum P (mg/dl)	**Range**	4.2 – 8.8	3.5 – 6.1	18.39	0.001*
	Mean ± SD	5.95 ± 1.03	4.71 ± 0.77		
Alkaline phosphatise (U/L)	**Range**	85-640	55-123	1.823	0.079
	Mean ± SD	202.53 ± 155.6	86.2 ± 6.88		
PTH (pg/ml)	**Range**	602 – 2220	23-63	7.63	0.001*
	Mean ± SD	1115.73 ± 140.53	43.93 ± 12.59		

P. Value < 0.05 significant; HB: haemoglobin %; HCT: Hematocrite value; PLT: Platelet count; BUN: blood urea nitrogen; Ca: calcium; P: phosphorus; K: potassium; PTH: paraathormone.

when compared to control group (P<0.05). There was a highly significant increase in PTH of patients as compared to controls (P<0.001).

Table 4: Serum levels of sex hormones in the studied patients and control groups.

		Patients	**Controls**	**T. test**	**P. value**
Serum FSH (mIU/ml)	Range	0.3 – 1.7	1.2 – 3.7	3.11	0.021*
	Mean ± SD	1.36 ± 0.22	2.64 ± 0.81		
Serum LH (mIU/ml	Range	0.1– 0.15	0.2– 3.4	5.21	0.003*
	Mean ± SD	0.11 ± 0.006	1.78± 1.12		
Serum female Estradiol (pg/ml)	Range	1.1 – 57.2	2.7 – 74.6	5.071	0.037*
	Mean ± SD	26.69 ± 21.59	51.03 ± 26.50		

P. Value < 0.05 significant

Table 4 clarified serum levels of sex hormones in the studied patients and control groups, There were significantly lower serum FSH, LH, and estrogen levels in Group I compared with Group II. Mean FSH level was 1.36 ± 0.22 mIU/mL in Group I vs. 2.64 ± 0.81 mIU/Ml in Group II with a p value of 0.021. Mean LH level was 0.11 ± 0.006 mIU/mL in Group I *vs.* 1.78 ± 1.12 mIU/mL in Group II with p value of 0.003.Mean estrogen level was 26.69 ± 21.59 pg/mL in Group I *vs.* 51.03 ± 26.50 pg/mL in Group II with p value of 0.037*.

Table 5 showed correlations between the dialysis duration and serum sex hormones levels in the studied patents group. There were significant negative correlations between serum FSH, LH and estrogen and dialysis duration (in days) (Figures 1–3).

Table 6 analyzed factors affecting hypogonadism in our studied patients group, duration of hemodialysis was found to be a significant cause of hypogonadism in Group I using univariate analysis.

Table 5: Correlation between the dialysis duration and serum sex hormones levels in the studied patents group.

	Correlation	
	R value	P value
Serum FSH (mIU/ml)	-0.835	0.01*
Serum LH (mIU/ml)	-0.597	0.01*
Serum female Estradiol (pg/ml)	0.624	0.01*

P. Value < 0.05 significant

Table 6: Univariate and multivariate analysis of factors affecting hypogonadism in studied patient group.

	UnivaiateP	**Mutivaiate**		
		P	**RR**	**95% CI**
Dialysis duration(40 patients >3 years)	0.002	0.007	2.4	1.5-8.5
ESRD complicated by hypothyroidism(3 patients)	0.21	0.23	2.1	1.2-6.5
ESRD caused by diabetic nephropathy(2 patients)	0.32	0.64	3.2	1.6-5.4
ESRD complicated by zinc deficiency (6 patients)	0.45	0.34	3.6	1.1-4.9

RR=Risk ratio; CI=Cofidence Interval

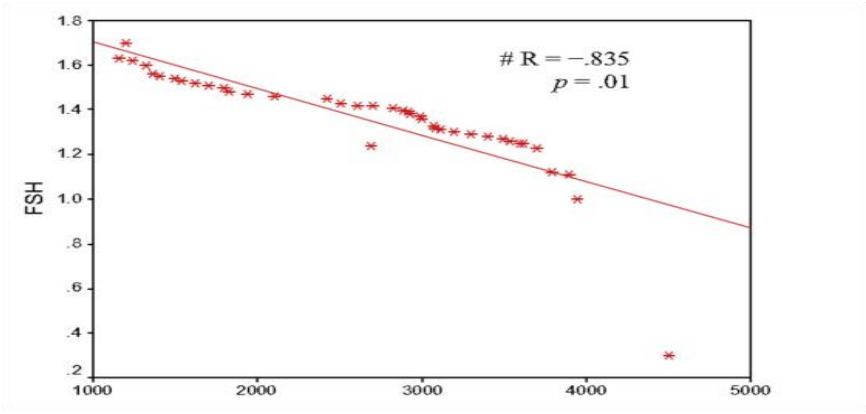

Figure 1: Correlation between serum FSH level (in mIU/ml) and dialysis duration (in days).

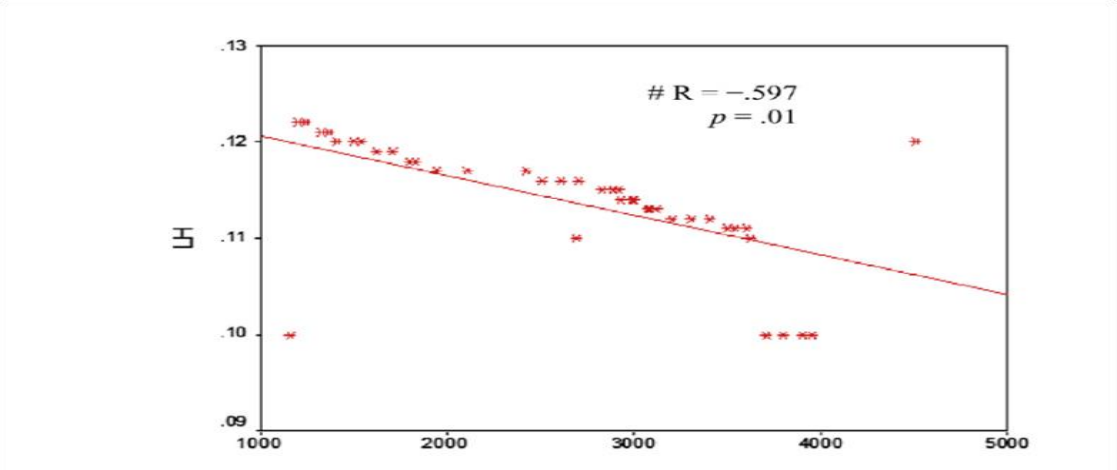

Figure 2: Correlation between serum LH level (in mIU/ml) and dialysis duration (in days).

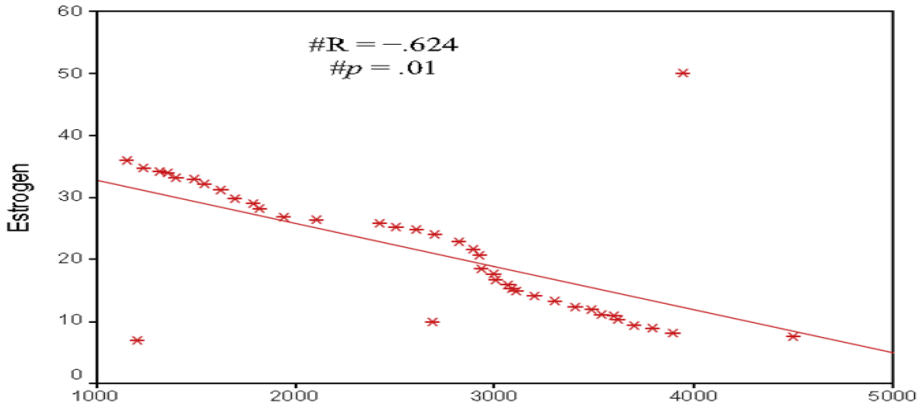

Figure 3: Correlation between serum serum estrogen level (in pg/ml) and dialysis duration (in days).

DISCUSSION

CRF was found to be associated with gonadal damage and decreased estradiol levels together with impaired regulation of gonadotropin secretion (Palmer, 1999). In the present study, laboratory assessment of serum FSH, LH and estradiol levels were done in order to assess whether gonadal dysfunctions occur in female children and adolescents with ESRD on regular hemodialysis therapy. In pediatric patients with CRF, only few studies have been performed to evaluate the status of the hypothalamo-pituitary-gonadal axis. Most of these deal with the endocrine changes that occur during adolescence (Armanini, *et al*., 2004).

Growth parameters were evaluated in the current study revealing that all anthropometric measurements (weight, height, BMI and MAC) were significantly lower in patients group when compared to healthy girls.

These results were supportive for previous data collected from multiple centers showing that children with ESRD had poor growth and lower BMI if compared with healthy children in general population (Haffner, *et al*., 1998; Berard, *et al*., 1981 and Wong, *et al*., 2000).

The patients in our study exhibited significantly lower Hb% and Hct value than in controls. This was in agreement with Harmon and Jabs, 1998 who reported that CRF was followed by renal anemia, which had been contributed to several factors as erythropoietin deficiency, decrease erythrocyte survival and increase blood loss (Harmon, *et al*., 1998).

In the current study, there was delayed puberty in Group I when compared with Group II with regards to Tanner staging. This is in agreement with Harold *et al.* 1983, Giusti et al., 1993 and Castellano *et al.*, 1993 who stated that pubertal progression occurred in dialyzed uremic children but it was delayed for chronological age (Haffner, *et al*., 1998; Giusti, *et al*., 1993 and Castellano, *et al*., 1993).

Our results were in agreement also with Rees L et al who concluded that half of the girls with CRF reach sexual maturity later than 95% of the normal population (Rees, *et al*., 1988).

Our results were in agreement also with Ehrich *et al.*, who concluded that, at least 50% of adolescents with ESRD entered puberty later than the normal range and achieved the pubertal milestones beyond the normal age range (Ehrich, *et al*., 1991).

In our study serum FSH, LH and estrsdiol levels were found significantly lower in patients than in controls, which was in agreement with Lim, 1980, Oertel *et al.*, 1983, Ferraris, 1987 and Giusti *et al.*, 1993 who stated that serum estrsdiol levels were lower in cases of CRF with or without dialysis (Lim, *et al*., 1980; Oertel, *et al*., 1983; Ferraris, *et al*., 1987 and Giusti, *et al*., 1993).

Our results were in agreement also with Palmer at 1999 who attributed these results to primary gonadal damage, presence of circulating LH receptor inhibitor that might contribute to gonadal cell resistance and impaired feedback mechanism at the hypothalamic pituitary level, in addition to presence of hyperprolacinemia (Palmer, 1999).

Many previous publications searched for hypogonadism associated with anemia in chronic illness like CKD. Rizzoni, *et al.*, 1986, reported that secondary gonadal failure might be due to siderosis of the pituitary gland or primary gonadal failure, which occurred secondary to iron deposition in ovaries due to repeated blood transfusion and iron overload resulting from chronic hemolytic anemia as a presentation of ESRD (Rizzoni, *et al*., 1986).

Palmer, 1999 stated that disturbances in pituitary-gonadal axis rarely normalize with initiation of hemodialysis or peritoneal dialysis, moreover, they may progress that matching with our study. This was explained that plasticizers in dialysis tubing, such as phytate may play a role in propagating the abnormalities in pituitary-gonadal axis (Palmer, 1999).

In the current study, serum levels of LH, FSH, and estrogen were significantly lower in Group I compared with Group II. These findings may be explained by uremic deposition in secretory cell of endocrine glands such as gonadotrophin cell of the pituitary gland that leads to the impairment of gonadal hormone secretion including FSH and LH.

In the current study, there were significant negative correlations between serum estrogen, LH, FSH, and dialysis duration. This could be explained by progressive damage of the pituitary gland with a subsequent decrease of gonadal hormones with a progressive increase in duration of disease, as the ovaries are vulnerable to the toxic effect of uremia even if it is not persistent with continuous removal by regular hemodialysis sessions leading to deficiency of estrogen hormone secretion. Using univariate and multivariate analysis of factors affecting hypogonadism in our study, the dialysis duration was the only significant with no other

associated factors e.g. hypothyroidism, type 1 diabetes mellitus or zinc deficiency, This was not in agreement with Al-Rimawi, *et al.,* who reported common associations of causes for hypogonadism in their study (Al-Rimawi, *et al*., 2005).

Recent explanation for delayed pubery in dialysis patients is abnormalities in magnesium homeostasis. Under physiological conditions, magnesium serves as a physiological regulator of multicatalytic proteinase complex (MPC) activities of the pituitary leading to stimulation of adenohypophyseal-gonadal function which control gonadal hormonal levels (Pereira, *et al*., 1992)

There was controversies regarding effects of magnesium on gonadal hormones, Zofková, *et al.* studied the effect of acute hypermagnesemia on LHRH-induced secretion of FSH, LH, prolactin, sex hormone and intact PTH and found that Gonadotropin secretion was not altered but added that quiescent sex hormone levels decreased moderately and PTH levels markedly dropped although in hypermagnesemia no correlations between the levels of PTH and those of magnesium, calcium and phosphorus could be found, in normomagnesemia significant correlations were confirmed between the levels of PTH and magnesemia. So magnesium in supraphysiologic concentrations does not significantly change the function of the adenohypophyseal-gonadal axis (Zofková, *et al*., 1993).

Some data suggest that combined Ca and Mg therapy was possibly more effective than calcium carbonate in the control of hyperphosphatemia in dialysis patients with good clinical and biological tolerance and without increasing the calcium levels (Helal, *et al*., 2016 and Misra, *et al*., 2017).

Carpenter, *et al.,* 2006, had carried out a pilot study demonstrating a positive effect of Mg supplementation for 12 months on accrual of bone mass in peripubertal Caucasian girls selected for suboptimal daily Mg intake. The supplement was well tolerated and safe. This study will serve as a model for designing future studies on skeletal effects of Mg in children (Carpenter, *et al*., 2006).

Furthermore, it is important to clarify to what degree serum magnesium levels can be safely elevated in pediatric patients with end stage renal disease undergoing HD since excessively high serum magnesium levels may also be harmful (Sakaguchi, *et al*., 2014).

Previously, authors investigated the impact of the changing estrogen and progesterone secretion on the parathyroid glands and the changes in serum magnesium levels during different phases of the menstrual cycle in healthy females. They found subtle but significant variations in Mg levels where the serum magnesium level was lowest in the follicular phase. Sonu reported that lower serum estrogen levels is associated with higher serum magnesium and urinary magnesium /creatinine ratio compared to healthy controls (Sonu, *et al*., 2016).

Several studies have reported that hypermagnesemia in hemodialysis patients plays a role for inhibition of PTH secretion, presenting a significant linear inverse correlation between PTH and magnesium thus lower serum Ca levels in these patients compared to controls (Lee, *et al*., 2016 and Massy, et al., 2016).

CONCLUSIONS

Female patients with ESRD may have gonadal hormones deficiency with a significant negative correlation between gonadal hormones including FSH, LH, estrogen, and duration of hemodialysis so pubertal development of female children and adolescents with ESRD is usually delayed as proven by decreased FSH,LH and Estradiol hormones levels which suggest a state of hypogonadism. Nutritional therapy especially optimizing protein intake to prevent hypoproteinemia, adequate dialysis and correction of anemia are clinical trials of controversy and worthy of considering optimizing pubertal development until these patients are transplanted.

RECOMMENDATIONS

It is necessary to regularly follow up female children with ESRD for assessment of puberty for early detection of endocrinal complications, as they are more vulnerable to develop hypogonadism and may require hormonal replacement therapy to improve their quality of

life. Keeping hemoglobin level within normal is recommended for normal pubertal development. Patients with delayed puberty are in need to be further investigated to measure FSH and LH to assess hypothalamic pituitary gonadal axis.

REFERENCES

1. Al-Rimawi, HS; Jallad, MF; Amarin, ZO and Obeidat, BR (2005) "Hypothalamic-pituitary-gonadal function in adolescent females with beta-thalassemia major". ***Int J Gynaecol Obstet*** 90: 44–47.
2. Anderson, SE; Dallal, GE and Must, A; (2003) "Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart**"**. ***Pediatrics*** 111: 844–850.
3. Armanini, D; Mattarello, MJ; Fiore, C; Bonanni, G; Scaroni, C; Sartorato, P and Palermo, M (2004) "Licorice reduces serum testosterone in healthy women**"**. ***Steroids*** 69: 763-766.
4. Berard, E; Crosnier, H; Six-Beneton, A; Chevallier, T; Cochat, P and Broyer, M (1981) "Recombinant human growth hormone treatment of children on hemodialysis". ***Ped Nephro*** 12: 304-310.
5. Carpenter, TO; DeLucia, MC; Zhang, JH; Bejnerowicz, G; Tartamella, L; Dziura, J; Petersen, KF; Befroy, D and Cohen, D (2006) "A Randomized Controlled Study of Effects of Dietary Magnesium Oxide Supplementation on Bone Mineral Content in Healthy Girls". ***J Clin Endocrinol Metab*** 91: 4866–4872.
6. Castellano, M; Turconi, A; Chaler, E; Rivarola, MA and Belgorosky, A (1993) "Hypothalamic-pituitary-gonadal function in prepubertal boys and girls with chronic renal failure**"**. ***J Pediatr*** 122: 46-51.
7. Chan, JCM; Williams, DM and Roth, KS (2002) "Kidney Failure in Infants and Children". ***Pediatr Rev*** 23: 47-60.

8. Choccalingam, C; Radha, RKN and Snigdha, N (2017) "Estimation of Platelet Counts and Other Hematological Parameters in Pseudothrombocytopenia Using Alternative Anticoagulant: Magnesium Sulfate". ***Clin Med Insights Blood Disord*** 10: 1–6.
9. Dötsch, J; Nüsken, K; Benz, K; Dittrich, K; Plank, Ch; Sauerstein, K and Rascher, W (2004) "Endocrine Dysregulation in Adolescents with Chronic Renal Failure". ***Transplantations Medizin*** 16.
10. Ehrich, JH; Rizzoni, G; Brunner, FP; Brynger, H; Geerlings, W; Fassbinder, W; Raine, AE; Selwood, NH and Tufveson G (1991) "Combined report on regular dialysis and transplantation in Europe, 1989". ***Nephrol Dial Transplant*** 6: 37–47.
11. Eugster, EA and Pescovitz, OH (2001) "Delayed puberty". In Endocrinology Degroot LJ et al. (eds):4th ed. 4,W.B. ***Saunders Company***, pp: 2023-2031.
12. Ferraris, JR; Domene, HM; Escobar, ME; Caletti, MG; Ramirez, JA and Rivarola, MA (1987) "Hormonal profile in pubertal females with chronic renal failure: before and under haemodialysis and after renal transplantation". ***Acta Endocrinol (Copenh)*** 115: 289–296.
13. Garibaldi, L (2004) "Physiology of Puberty**"**. In: Behrman RE, Kliegman RM. Nelson, Text Book of pediatrics, 17 edition. Chapter 555, pp: 1862-1864.
14. George-Gay, B and Parker, K (2003) "Understanding the complete blood count with differential". ***J Perianesth Nurs*** 18: 96–114.
15. Gilbert-Barness, E and Barness, LA (2003) "Clinical Use of Pediatric Diagnostic Tests", 1st Edition. Lippincott Williams & Wilkins P 689, Printer: ***Maple Press***.
16. Giusti, M; Perfumo, F and Verrina, E (1993) "Delayed puberty in uremia: pituitary-gonadal function during short-term pulsatile luteinizing hormone releasing hormone administration". ***J Endocrinol Invest*** 15: 709-717.
17. Gupta, V and Lee, M (2012) "Growth hormone in chronic renal disease". ***Indian J Endocrinol Metab*** 16: 195-203.
18. Haffner, D; Wuhl, E; Schaefer, F; Nissel, R; Tonshoff, B and Mehls, O (1998) "The German study group for growth hormone treatment in CRF". ***J Am Soc Nephrol*** 9: 1899-1907.

19. Harmon, WE and Jabs, KL (1998) "Chronic renal failure". In: Paediatric Nephrology. 4th edition, ***Williams and Wilkins*** pp: 1151-1154.

20. Helal, I; Elkateb, H; Hedri, H; Hajri, M and Ben Hamida, F (2016) "Efficacy and Safety of Calcium Acetate–Magnesium Carbonate in theTreatment of Hyperphosphatemia in Dialysis Patients". ***Saudi J Kidney Dis Transpl*** 27: 1162-1167.

21. Kail, RV and Cavanaugh, JC (2010) "Human Development: A Lifespan View (5th ed.)**"** ***Cengage Learning*** pp: 296.

22. Khothari, CR (2012) "Research methodology, methods and Techniques", New Age International, In: Khothari CR(ed). New Delhi: 2nd ed, pp: 95-97.

23. Lee, S; Ryu, J; Kim, S; Ryu, D; Kang, D and Choi, KB (2016) "The Relationship between Magnesium and Endothelial Function in End-Stage Renal Disease Patients on Hemodialysis". ***Yonsei Med J*** 57: 1446-1453.

24. Lim, VS; Henriquez, C; Sievertsen, G and Frohman, LA (1980) "Ovarian function in chronic renal failure: Evidence suggesting hypothalamic anovulation". ***Ann Intern Med*** 93: 21-27.

25. Massy, ZA; Nistor, I; Apetrii, M; Brandenburg, VM; Bover, J and Evenepoel, P (2016) "Magnesium-based interventions for normal kidney function and chronic kidney disease". ***Magnesium Res*** 29: 126-140.

26. Misra, PS and Nessim, SJ (2017) "Clinical aspects of magnesium physiology in patients on Dialysis". ***Seminars in Dialysis*** pp: 1–8.

27. Oertel, PJ; Lichtwald, K; Häffner, S; Rauh, W; Schönberg, D and Schärer, K (1983) "Hypothalamo-pituitary-gonadal axis in children with chronic renal failure". ***Kidney Int*** 24: 34–39

28. Palin, WEJ; von Fraunhofer, JA and Smith, DJJ (1986) "Measurement of breast volume: comparison of techniques". ***Plast Reconstr Surg*** 77: 253–255.

29. Palmer, BF (1999) "Sexual Dysfunction in Uremia". ***J Am Soc Nephrol*** 10: 1381–1388.

30. Pereira, ME; Yu, B and Wilk, S (1992) "Enzymatic changes of the bovine pituitary multicatalytic proteinase complex, induced by magnesium ions**"**. ***Arch Biochem Biophys*** 294: 1-8.

31. Plant TM (2001) "Leptin, growth hormone, and the onset of primate puberty**"**. ***J Clin Endocrinol Metab*** 86: 458–460.

32. Rees, L; Greene, SA; Adlard, P; Jones, J; Haycock, GB; Rigden, SP; Preece, M and Chantler, C (1988) "Growth and endocrine function after renal transplantation". ***Arch Dis Child*** 63: 1326–1332.

33. Rizzoni, G, Broyer, M; Brunner, FP; Brynger, H; Challah, S; Oulès, R; Rizzoni, G; Selwood, NH; Wing, AJ and Balás, EA (1986) "Combined report on regular hemodialysis and transplantation in Europe, 1985". ***Proc EDTA*** 23: 55–83.

34. Romero-Corral, A; Somers, VK; Sierra-Johnson, J; Thomas, RJ; Collazo-Clavell, ML; Korinek, J; Allison, TG; Batsis, JA; Sert-Kuniyoshi, FH and Lopez-Jimenez, F (2008) "Accuracy of body mass index in diagnosing obesity in the adult general population". ***Int J Obes*** 32: 959-966.

35. Sakaguchi, Y; Fujii, N; Shoji, T; Hayashi, T; Rakugi, H and Isaka, Y (2014) "Hypomagnesemia is a significant predictor of cardiovascular and non-cardiovascular mortality in patients undergoing hemodialysis". ***Kidney Int*** 85: 174–181.

36. Sonu, Y; Avinash, SS; Kumar, KA; Malathi, M and Shivashankara, AR (2016) "Effect of Oestrogen on Altering the Serum and Urinary Levels of Calcium, Phosphate and Magnesium in Hysterectomised Women Compared to Natural Menopausal South Indian Women:A Case Control Study". ***Ind J Clin Biochem*** 31: 326–331

37. Sun, Y; Tao, FB and Su, PY (2012) "China Puberty Research Collaboration.Self-assessment of pubertal Tanner stage by realistic color images in representative Chinese obese and non-obese children and adolescents". ***Acta Paediatr*** 101: e163-e166.

38. Tanner, JM and Whitehouse, RH (1976) "A note on the bone age at which patients with true isolated GH deficiency enter puberty". ***J Clin Endocrinol Meta*** 41:788.

39. Wide, L (1981) "Electrophoretic and gel chromatographic analyses of follicle stimulating hormone in human serum". ***Ups J Med Sci*** 86: 249–258.

40. Wong, CS; Gipson, DS; Gillen, DL; Emerson, S; Koepsell, T, Sherrard, DJ; Watkins, SL and Breen, CS (2000) "Anthropometric measures and risk of death in children with ESRD". ***J Kidney Dis*** 36: 811-819.

41. Zofková, I; Lamberg-Allardt, C; Kancheva, RL and Stárka, L (1993) "Effect of hypermagnesemia on the adenohypophyseal-gonadal function, parathyroid hormone secretion and some other hormonal indicators". ***Horm Metab Res*** 25: 29-33

Corresponding Author:

Dr. Mohamed A.El-Gamasy

Assistant Professer of Pediatrics, Faculty of Medicine, Tanta University Hospital, Pediatric department,,El Giesh Street, Tanta, Gharbia, Egypt

Email: mgamsy@gmail.com

Fax: +20403333666

Tel: +201208136076

Cite This Article: El-Gamasy, MA; Abdelmageed, MM and Abd Ellatif, MN (2017), "Study of gonadal hormones in Egyptian female children with End Stage Renal Disease under regular haemodialysis in correlation with dialysis duration." ***International Journal of Drug Research and Technology*** Vol. 7 (5), 234-254.

INTERNATIONAL JOURNAL OF DRUG RESEARCH AND TECHNOLOGY