### PITUITARY GONADAL ABNORMALITIES IN EGYPTIAN CHILDREN AND ADOLESCENTS WITH CHRONIC RENAL INSUFFICIENCY

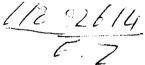
#### **Thesis**

submitted for partial fulfillment of MD Degree in Paediatrics

# Ihab Zaki F. El Hakim

M.B., B. Ch., MS Paediatrics Assistant lecturer of Paediatrics,

Faculty of Medicine, Ain Shams University.



#### Supervised by

# Prof. Dr. Farida Ahmad Farid

Professor of Paediatrics, Faculty of Medicine, Ain Shams University.

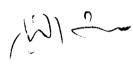


53 W25

#### Assistant supervisors

#### Dr. Khaled Salah Awwad

(1)0100 (an 10100 Assistant professor of Paediatrics, Faculty of Medicine, Ain Shams University.



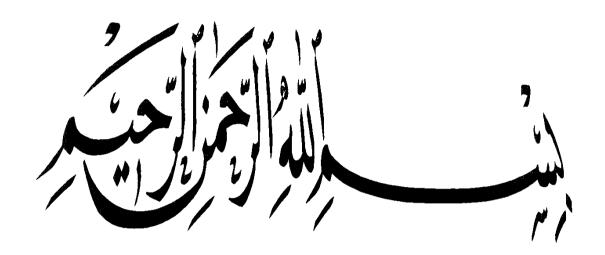
# Dr. Mohammed S. El Din Faheem

Lecturer of Paediatrics, Faculty of Medicine, Ain Shams University.

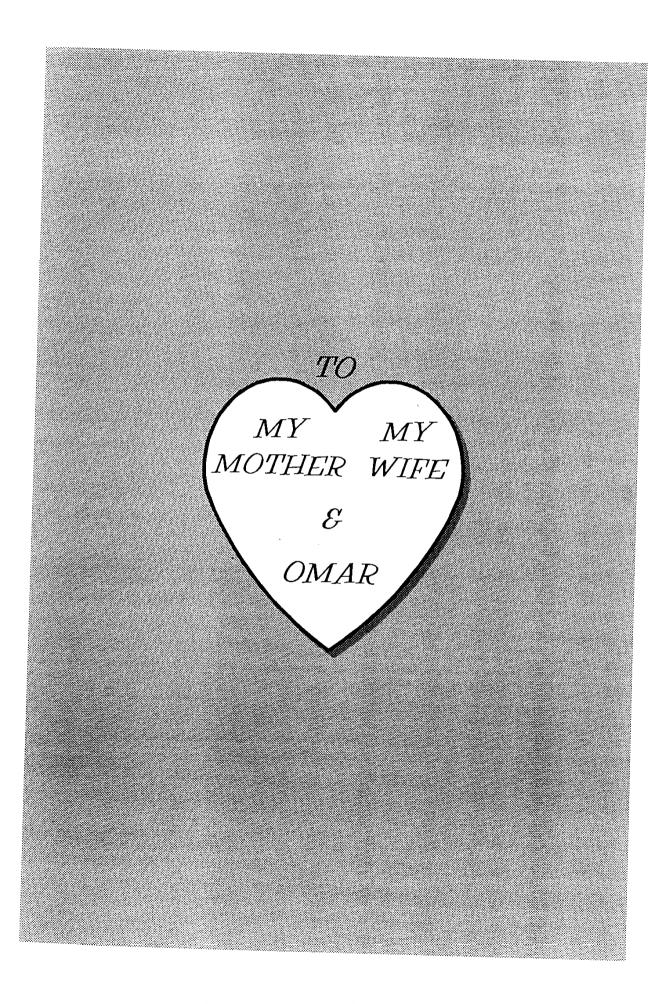
# Dr. Taher Mohammed Farid

Lecturer of Biochemistry, Faculty of Medicine, Ain Shams University.

> Cairo 1995







### Acknowledgment

First and foremost thanks are to Allah, The Most Beneficent and Merciful.

I must state here the debt I owe to Dr. Farida Ahmad Farid, Professor of Paediatrics, Ain Shams University, for her constructive remarks and valuable advice. Working under her supervision is all at once both pleasurable and educational. Her motherly altitude lowards her patients and her team is unique and memorable.

To Dr. Khaled Salah Awwad, Assistant professor of Paediatrics, Ain Shams university I would like to express my cordial thanks and sincere gratitude; he gave me an excellent example of how a true scientist should guide and supervise his student's work.

I would like also to extend my deep appreciation to Dr. Mohammed S. El Din Faheem, Lecturer of Paediatrics, Sin Shams University, for his endless encouragement and constructive criticism with the spirit and capacity of a true scholar.

This work would have never been completed without the great help, close supervision and meticulous lab work offered by Dr. Taher Mohammed Farid, Lecturer of Biochemistry, Ain Shams University.

Any expression of thanks would fail to give the team of the Paediatric Dialysis Unit, Ain Shams university, its worth of gratitude for its practical and moral support throughout this work. Also the team of the Oncology Diagnostic Unit deserves a special thank for the help given during the practical part of this thesis.

Last but by no means least, I acknowledge my courageous patients and their brave parents for their cooperation and their sincere feelings. I also acknowledge all my senior and junior colleagues who helped me in one way or another in achieving this work.

Ihab El Hakim

#### **CONTENTS**

List of abbreviations————————————————————————————————————	i
List of tables—	
List of figures—	
Introduction————————————————————————————————————	1
Aim of the work————————————————————————————————————	
Review of literature————————————————————————————————————	3
Sexual maturation	
Terminology—	3
Physiology———————————————————————————————————	
Physical changes—————————	??
Behavioral changes————————————————————————————————————	27
Disorders of puberty—	28
Chronic renal failure	
definition—————————————————————————————————	31
Stages of the disease—	31
Epidemiology———————————————————————————————————	32
Causes————————	32
Prognosis-	33
Pathogenesis of some clinico-metabolic changes—	<del>37</del>
Conservative management—	46
Dialysis therapy————————————————————————————————————	—— <u>-4</u> 8
Sexual maturation in chronic renal failure	
Disorders in the male—	60
Disorders in the female—	65
Sexual maturation in CRF————————————————————————————————————	——67
Subjects and methods————————————————————————————————————	69
Results	86
Discussion———————————————————————————————————	130
Recommendations————————————————————————————————————	148
Summary & conclusion————————————————————————————————————	140
References	152
Arabic summary	

#### **LIST OF ABBREVIATIONS**

μl microlitre

<sup>51</sup>Cr-EDTA chromium 51-ethylene diamine tetracetate 99Tc-DTPA technitium 99-diethylene triamine pentacetate

A-V arterio-venous

**ABP** arterial blood pressure

**ACE** angiotensin converting enzyme **ACTH** adrenocorticotropic hormone

**ADH** antidiuretic hormone ANP atrial natriuretic peptide

В bromocriptine BP blood pressure C clomiphene citrate

CAPD continuous ambulatory peritoneal dialysis

**CCB** calcium channel blocker

**CCPD** continuous cycler-assisted peritoneal dialysis

Ccr creatinine clearance

**CGN** chronic glomerulonephritis **CNS** central nervous system

CO cardiac output CRF chronic renal failure **DHEA** dehydroepiandrosterone

**DHEAS** dehydroepiandrosterone sulfate

DHT dihydrotestosterone

e.g. for example

ELISA enzyme-linked immunosorbent assay

**ESRD** end stage renal disease

**ESTR** estradiol F female

**FSH** follicle-stimulating hormone **GFR** glomerular filtration rate

GH growth hormone H<sub>2</sub>SO<sub>4</sub> sulfuric acid **HCG** 

human chorionic gonadotropin

HC1 hydrochloric acid HD haemodialysis

HDL high density lipoprotein HRP horseradish peroxidase HS highly significant

**HSP** Henoch-Shoenlein purpura

Ht. height i.e. that is to say

IGF I insulin-like growth factor I

ПЛ international unit K

potassium Kg kilogram

LBW low birth weight

LDL low density lipoprotein LH leuteinizing hormone LHRH

leuteinizing hormone-releasing hormone

M male

**MEIA** microparticle enzyme immunoassay

**MENS** menstruation mEq milliequivalent mg milligram min. minute

mIU milli-international unit

ml millilitre

**MRI** magnetic resonance imaging

Na sodium

NB neurogenic bladder

ng nanogram nm nanometer NS not significant OD optical density OH hydroxy

**PCK** polycystic kidney

pg picogram PG prostaglandin

PHI-27 peptide-histidine-isoleucine-27

PRL prolactin

PTFE poly-tetra-fluoro-ethylene PTH parathyroid hormone **RLU** relative light unit S

significant

Scr serum creatinine SD standard deviation sec.

second

SMR sexual maturity rating

SN serial number triiodothyronine

T4 thyroxin testosterone

TMB
TMP
trans-membrane pressure
trans-membrane pressure
total peripheral resistance
thyrotropin-releasing hormone
thyrotropin-releasing hormone
thyroid-stimulating hormone

TTP thrombotic thrombocytopaenic purpura

USA
UTI
The United States of America

urinary tract infection

VIP vasoactive intestinal peptide

versus versus

WHO world health organization

y year

# List of tables

Table 1: Postulated ontogeny of the homest state in the state of the homest state of t	
Table 1: Postulated ontogeny of the hypothalamic-pituitary-gonadal circuit  Table 2: Classification of Sex Maturity Stages in Girls  Table 3: Classification of Sex Maturity Stages in Boys	17
Table 3: Classification of Son Man 200	23
Table 4: Classification of delevant 1 1 Boys.	24
Table 5: Classification of savuel and the state infantifish	20
Table 6: Effect of Decreasing D. 125	30
Table /: Aetiology of ECDD: 111	3.2
Table 8: Aetiology of ESPD: F	3.4
Table 9. Plasma creatining level	3.5
Table 10: Mean and Range of the Control of the Cont	36
in Normal Children and Voyage A. L. Color and Estimating Creatinine Clearance	<b>_</b>
Table 11: Factors that Impact on DI	36
Table 12: Agents/Treatment above to the state of the stat	41
Tailure. Progression of chronic renal	
Table 13: Complications from permanent HD access.  Table 14: Maximum concentrations of contaminants permitted in water and 15 minutes of the contaminant permitted in water and 15 minutes of the contaminants permitted in water and 15 minutes of the contaminants permitted in water and 15 minutes of the contaminants permitted in water and 15 minutes of the contaminants permitted in water and 15 minutes of the contaminants permitted in water and 15 minutes of the contaminants permitted in water and 15 minutes of the contaminant perm	46
Table 14: Maximum concentration 6	51
preparation of dialyanta	
Table 15: Initial heparin dose for HD in children	53
1 able 10. Advantages and dis-1	5.5
1 4010 17. Common clinical and 11	5.6
Table 18: Drugs that may course at the second secon	50
Table 18: Drugs that may cause sexual dysfunction.  Table 19: Patients' selection & drug therapy.	64
Table 19: Patients' selection & drug therapy.  Tables of results:	85
Table I: Clinical data of females on conservative treatment (group IF)	
Table II: Laboratory data of females on conservative treatment (group IF)	86
Table III: Clinical data of malas and the real factor of the control of the contr	86
Table IV: Laboratory data of 1	97
Table V. Clinical data of familiary and the determining (group IVI)	Ω7
Table VI: Laboratory data of family	QQ
Table VII. Clinical data of malas and the group HT)	88
Table VIII: Lahoratory data at 1	90
Table IX: Clinical data of famala (group II IVI)	20
Table X: Laboratory data of fam. 1	00
Table Al. Clinical data of mala and the company of the formation of the company o	۵Λ
Table All: Laboratory data of	0.1
140le Alli Comparison of many 1	Ω1
Table AIV: Aethology of CDE: 11	റാ
1 aut AV. Comparison of many 1	$\Omega A$
Table XVI: Comparison of the 3 male groups regarding erection.	96
regarding erection.	97
	) /

Table XVII: Comparison of the 3 male groups regarding ejaculation
Table XVIII: Comparison between mean values of SMR (breast) in female groups. 99  Table XV: Comparison between mean values of SMR (pubic hair) in female groups. 99
A WOLC MIN COMPANION Lat
Auto AA. Comparison between the control of the cont
The AMI. Comparison has the second of the se
The following the body of the state of the s
Auto Mail Comparison by
TANK COMPANION L.
Table 201 V. Comparison L.
Table XXVI: Hormand at the Table XXVI: Hormand at the Table XXVIII Hormand at the Tabl
Table XXVIII Comments status of the studied groups
Table XXVII: Comparison between mean values of GFR in various groups
= "" \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \
A WOLD AMARIA COMPARISON L.
- word MAA. Comparison Lat
- word 2000 to the term to the term of the
- WOLC MANIE FITTER OF AT ALL
- WOLV ALA ALL I ABONO L I I I I I I I I I I I I I I I I I I
Table XXXIII: Laboratory data before and after renal transplantation and the mean of
male control
129

### **List of Figures**

Figure 1: Chemical structure of LHRH	
Figure 1: Chemical structure of LHRH.  Figure 2: Biosynthesis and metabolism of estrogens.  Figure 3: Biosynthesis and metabolism of testosterons.	5
Figure 3: Biosynthesis and metabolisms of the strongers.	7
Figure 4: Structure of human protection	9
Figure 5: Regulation of gonadotronia	10
Figure 6: Regulation of gonadotronia	12
Figure 6: Regulation of gonadotropin secretion in the human female.  Figure 7: The changing pattern of serum gonadotropins and seed to the service of the se	
life to maturity	etal
life to maturity	
Figure 9: Standard curve of absorbance	70
Figure 9: Standard curve of absorbance vs. concentration.  Figure 10: Chemiluminescence immunoassay-sandwich reaction.	
Sundy Sundy Chi Teachon	79
Figures of results:	
Figure 1. 3.6	
Figure I: Mean values of age of different groups.  Figure II: Aetiology of CRF in all patients collectively.	0.0
Figure II: Aetiology of CRF in all patients collectively.  Figure III: Aetiology of CRF in the studied groups separately.	
Figure III: Aetiology of CRF in the studied groups separately.  Figure IV: Menarche in different female groups.	
Figure IV: Menarche in different female groups.  Figure V: Erection in different male groups.	95
Figure V: Erection in different male groups.  Figure VI: Ejaculation in different male groups	96
Figure VI: Ejaculation in different male groups.  Figure VII: SMR (breast) in females of different groups	98
Figure VII: SMR (breast) in females of different groups.  Figure VIII: SMR (pubic hair) in females of different groups.	98
Figure VIII: SMR (pubic hair) in females of different groups.  Figure IX: SMR (pubic hair) in males of different groups.	100
Figure IX: SMR (pubic hair) in malar C 1:50	101
Figure X: Weight and height contiles:	101
Figure XI: Weight and height confiler in	102
rigure XII: Mean values of blood was in a state groups.	103
Figure XIII: Mean values of blood	106
Figure XIV: Mean values of serum organical mane groups	106
Figure XV: Mean values of some and it various remail groups.	107
Figure XVI: Mean values of GED in and the groups.	108
Figure XVII: Mean values of CED:	109
Figure XVIII: Mean values of FSU and LII: 41 - 60 - 60 - 60 - 60 - 60 - 60 - 60 - 6	109
Figure XIX: Mean values of FSH and III: 11 10 11 11 11 11 11 11 11 11 11 11 11	113
Figure XX: Mean values of serum DDI:	113
Figure XXI: Mean values of service DDV	114
Figure XXII: Mean values of some Forms	115
rigure XXIII: Mean values of serum ECTD:	116
rigure XXIV: Mean values of server Tropy	117
Figure XXV: Mean values of some TEST:	118
Figure XXV: Mean values of serum TEST in various female groups.  Figure XXVI: Type of therapy given to patients of each group.	118
Figure XXVI: Type of therapy given to patients of each group.  Figure XXVII: Mean values of serum FSH before and after therapy.	110
Figure XXVII: Mean values of serum FSH before and after therapy	121
X 3	141

Figure XXVIII: Mean values of serum LH before and after therapy.  Figure XXIX: Mean values of serum PRL before and after therapy.	
Figure XXIX: Mean values of serum PRL before and after therapy.  Figure XXX: Mean values of serum ESTR before and after therapy.  Figure XXXIII	121
riguie AAX. Mean values of an Boom in the arter inclapy	122
Tiguie AXXI. Mean values of	122
Figure XXXII: Correlation between FSH and LH in group I F.  Figure XXXIII: Correlation between FSH and LH in group I F.  Figure XXXIII: Correlation between FSH and LH in group II F.	122
Figure XXXIII: Correlation between FSH and LH in group I F.	123
Figure XXXIV: Correlation between FSH and LH in group I F.  Figure XXXIV: Correlation between FSH and LH in group I M.  Figure XXXIV: Correlation between FSH and LH in group I M.	124
Figure XXXIV: Correlation between FSH and LH in group II F.  Figure XXXV: Correlation between FSH and LH in group I M.  Figure XXXVII. C. Figure XXVIII. C. Figure XXXVIII. C. Figure XXXVIIII. C. Figure XXXVIII. C. Figure X	124
Figure XXXV: Correlation between FSH and LH in group I M.  Figure XXXVI: Correlation between FSH and LH in group II M.  Figure XXXVIII. Correlation between FSH and urea in all patients	125
Figure XXXVI: Correlation between FSH and LH in group II M.  Figure XXXVII: Correlation between FSH and urea in all patients.  Figure XXXVIII: Correlation between FSH and creatining in all patients.	125
Figure XXXVII: Correlation between FSH and creatinine in all patients.  Figure XXXVIII: Correlation between FSH and GFR in all patients.  Figure XXXVIII: Correlation between FSH and GFR in all patients.	126
Figure XXXVIII: Correlation between FSH and GFR in all patients.  Figure XXXIX: Correlation between prolactin and creatining in all patients.	126
Figure XXXIX: Correlation between prolactin and creatinine in all patients.  Figure XL: Correlation between estradiol and LH in female patients.	127
Figure XL: Correlation between estradiol and LH in female notice to	127
Figure XL: Correlation between estradiol and LH in female patients.  Figure XLI: Correlation between estradiol and LH in female patients.	128
Tentale patients	. 128
Equation I: calculation of GFR from height and serum creatinine	
norght and serum creatinine	35

# Introduction

<u>Introduction</u>

The kidney is an important organ by which human life can adjust and maintain its own homeostasis. Kidney performs this job, not only by removal of waste and toxic by-products, but also through its hormonal and haemopoietic functions. So, homeostatic mal-adjustment is expected in case of renal insufficiency (Rees et al., 1989).

Chronic renal insufficiency is one of the serious problems in paediatric age group which was ultimately fatal. However, with the advent of maintenance haemodialysis for treatment of end-stage renal disease has resulted in a large population of survivors with chronic renal failure. Since the artificial kidney is at best a poor substitute for the real organ, not all symptoms of renal insufficiency are corrected. These residual symptoms together with the abnormalities iatrogenically created by dialysis, constitute the syndrome of chronic uraemia, characterized by anaemia, neuropathy, renal osteodystrophy, hyperlipidaemia and a number of endocrinopathies (Henning et al., 1988).

Although there is a few data documenting the hormonal status of uraemic children in the pubertal age, chronic renal failure is known to cause delayed sexual maturation. Several possibilities could theoretically account for this abnormality: a) Primary gonadal damage by uraemic toxins, b) Extreme sensitivity of the hypothalamo-pituitary axis to the inhibitory effect of gonadal steroids (Belgorosky et al., 1990).

Hyperprolactinaemia among patients with chronic renal failure, even among those on maintenance haemodialysis has a high incidence and is positively correlated to serum creatinine (Cowden et al., 1978). It seems to be caused by the progressive loss of the ability of the kidney to remove prolactin whether through urinary clearance or by tubular resorption and catabolization (Gomez et al., 1980). It may have a role in the problem of pubertal delay by interfering with leuteinizing hormone secretion (Rigden et al., 1990).