Study of Cardiac Functions in Children with Congenital Adrenal Hyperplasia

Thesis

For Partial Fulfillment of Master Degree in Pediatrics

By

Sylvia Safwat Nasseif

M.B. B.Ch. (2012)

Faculty of Medicine- Ain Shams University

Under Supervision of

Dr. Nermine Hussein Amr

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Omneya Ibrahim Youssef

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Dr. Nadin Nabil Toaima

Associate Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2019

Acknowledgment

First of all, all gratitude is due to **Allah** almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

I would like to express my deepest thanks, gratitude, and respect for **Prof. Dr. Nermine Hussein Amr** Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her continuous help and support. I was very fortunate to work under her supervision; she introduced me to a completely new field, and was extremely patient as I took my first stumbling steps in this thesis. Her close supervision made everything that much easier and that much possible.

My sincere thanks go to **Prof. Dr. Omneya Ibrahim Youssef**, Professor of Pediatrics, Faculty of Medicine Ain Shams University, for her continuous advice and supervision. I'm very grateful for her continuous encouragement and guidance.

I would also like to voice my gratitude for **Dr. Nadin Nabil Toaima,** Associate Professor of Pediatrics, Faculty of Medicine, Ain Shams University for her working so closely with me to make sure that everything goes as smoothly as possible. Her continuous help, encouragement, and attention to detail were a corner stone for this work to come to light. Special thanks for **Dr. Rana Abd El-Hakim** Lecturer of Pediatrics Ain Shams University for her contribution and help in the work.

My sincere thanks go to **Dr. Tareq Mostafa Kamal** Professor of Consultant of human genetics, Ain Shams University, for his continuous advice and supervision on genetic study. I'm very grateful for his continuous encouragement and guidance.

Last but not least, I dedicate this work to **my family,** especially **my Father and my Mother,** whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Contents

List of Abbreviations

ACTH	**:**	Adrenocorticotropic hormone
AIS	**:**	Androgen insensitivity syndrome
BCIP	**:**	Bromo-4-chloro-3-indolyl phosphate
BMI	**:**	Body mass index
BMI_{HA}	**:**	BMI-for-height-age
CAH	**:**	Congenital Adrenal Hyperplasia
CIMT	**:**	Carotid intima media thickness
CO	**:**	Assessment of cardiac output
CPP	**:**	Central Precociuos Puberty
CRH	**:**	Corticotropin releasing hormone
CV	**:**	Cardiovascular
CVD	**:**	Cardiovascular disease
DHEA	**:**	Dehydroepiandrosterone
DOC	**:**	Deoxycorticosterone
DSD	**:**	Disorder of sex development
ECG	**:**	Electrocardiogram
EDV	**:**	End-diastolic volume
EF	**:**	Ejection fraction
ESV	**:**	End systolic volume
ET	**:**	Divided by ejection time
FMD	**:**	Flow-mediated dilatation

FS	**:**	Fractional shortening
GnRH	**:**	Gonadotropin-releasing hormone
HC	**:**	Hydrocortisone
HFPEF	**:**	Heart failure with preserved ejection fraction
HPA	**:**	Hypothalamic pituitary adrenal
HRQoL	**:**	Health related quality of life
ICT	**:**	Isovolumic contraction time
IMT	**:**	Intima-media thickness
I R	**:**	Insulin Resistance
IRT	**:**	Isovolumic relaxation time
IVST	**:**	Interventricular septum thickness
kb	**:**	Kilobase pairs
LHRHa	**:**	Luteinizing Hormone Releasing Hormone analog
LV	**:**	Left ventricular
LVDD	**:**	Ventricular diastolic dysfunction
LVEDd	**:**	Ventricular end diastolic diameter
LVM	**:**	Left ventricular mass
LVMI	**:**	Left ventricular mass index
MPI	**:**	Myocardial performance index
NBT	**:**	Nitro blue tetrazolium
OH	**:**	Hydroxylase
PAI	**:**	Primary adrenal insufficiency

PH	**:**	Pulmonary hypertension
PMDS	**:**	Persistent mullerian duct syndrome
PPP	**:**	Pseudo Precocious Puberty
PRA	**:**	Plasma renin activity
PW	**:**	Pulsed-wave
QoL	**:**	Quality of life
RV	**:**	Right ventricular
SV	**:**	Simple virilizing
SW	**:**	Salt-wasting
TAPSE	**:**	Tricuspid annular plane systolic excursion
TARTs	**:**	Testicular adrenal rest tumors
TDI	**:**	Tissue Doppler Imaging
Tei	**:**	Myocardial performance index
TTE	**:**	Transthoracic echocardiography
17-OHP	**:**	17-hydroxyprogesterone
21OH	**:**	21-hydroxylase
21-OHD	**:**	21-hydroxylase-deficiency
2D	**:**	Two-dimensional
3β-HSD	**:**	3β-hydroxysteroid dehydrogenase

List of Tables

List of Figures

Introduction

Congenital adrenal hyperplasia (CAH) encompasses a group of inherited autosomal recessive diseases affecting adrenal steroid synthesis ***(White and Speiser, 2000)***.

The impaired cortisol secretion causes ACTH levels to rise and stimulate adrenocortical hormone secretion, resulting in adrenal hyperplasia, and increased production of androgens and steroid precursors before the enzymatic defect ***(Forest et al., 2005).***

The most frequent CAH variant, accounting for 95% of all affected patients, is 21- hydroxylase deficiency and caused by inactivating mutations in the 21- hydroxylase gene (P450c21) which is designated (CYP21) ***(White and Speiser, 2000).*** Deficiency in P450c21 activity prevents the conversion of 17-hydroxyprogesterone to 11-deoxycorticosterone **(*Hsien-Hsiung Lee et al., 1996*)**. Most patients are compound heterozygotes having different mutations of the CYP21 gene on each allele **(*Hsien-Hsiung Lee et al., 1996*).**

Two distinct phenotypes are recognized in CAH due to 21-OHD: Classical CAH, the most severe form comprises both salt- wasting (SW) and simple virilizing

(SV) forms, with a worldwide incidence of 1:15000 live births, and the Non-classical (NC) form which may be asymptomatic or associated with signs of postnatal or even adult onset androgen excess ***(Forest et al., 2005).***

Treatment of CAH consists of glucocorticoids (GCs) and, when necessary, mineralocorticoids to prevent adrenal crisis and to suppress the abnormal secretion of androgens and steroid precursors from the adrenal cortex **(*Oglivie et al., 2006*).** Lifelong glucocorticoid replacement therapy is often required in CAH patients to reduce adrenal androgen excess ***(King et al., 2006).***

The therapeutic spectrum of glucocorticoids is narrow and supra-physiological doses, are often needed to control the hyperandrogenism ***(Arlt et al., 2010).*** It has been suggested that patients with CAH develop unfavourable cardiovascular risk profile either because of the hyperandrogenism in untreated or undertreated patients or because of the supraphysiological doses of GCs used **(*Mooij et al., 2010*).**

Steroids contribute to elevated cardiovascular diseases partly by changing the levels of lipoproteins that carry cholesterol in blood by increasing levels of LDL and decreasing levels of HDL which may lead to heart attack or

stroke **(*Mooij et al., 2010*),** also can cause alteration in cardiac structure such as enlargement and thickening of the left ventricle which impairs normal contraction and relaxation of it *(cardiomyopathy)* all these may lead to hypertension, cardiac arrhythmias, congestive heart failure, heart attack and sudden cardiac arrest ***(Depiccoli et al., 1999).***

Aim of the Work

This study aims to evaluate echo-cardiographic functions in children with congenital adrenal hyperplasia receiving corticosteroid therapy for more than six years.