

High versus low dose adrenocorticotrophic hormone (ACTH) for evaluation of adrenocortical function in healthy, septic and respiratory distressed newborns

Summary of Thesis

Submitted for Fulfillment of Ph.D. In Childhood Studies

By Mohamed Saad Mohamed Hamido MBBCh, Master of Pediatrics

Supervisors Prof. Ashraf Tawfik Soliman

Prof. of Pediatrics Faculty of Medicine Alexandria University

Prof. Khaled Hussien Taman

Prof. of Pediatrics
Institute of Postgraduate Childhood Studies
Ain Shams University

Prof. Mohamed Mustafa Rizk

Prof. of Clinical Pathology Faculty of Medicine Alexandria University



High versus low dose adrenocorticotrophic hormone (ACTH) for evaluation of adrenocortical function in healthy, septic and respiratory distressed newborns

Thesis

Submitted for Fulfillment of Ph.D. In Childhood Studies

By Mohamed Saad Mohamed Hamido MBBCh, Master of Pediatrics

Supervisors Prof. Ashraf Tawfik Soliman

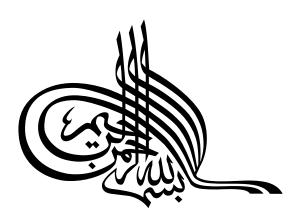
> Prof. of Pediatrics Faculty of Medicine Alexandria University

Prof. Khaled Hussien Taman

Prof. of Pediatrics
Institute of Postgraduate Childhood Studies
Ain Shams University

Prof. Mohamed Mustafa Rizk

Prof. of Clinical Pathology Faculty of Medicine Alexandria University



(وقل رب زدني علماً)

ACKNOLEDGMENT

Thanks to God for what was done in this work and elsewhere. It is a pleasure to express my deepest gratitude and appreciation to **Prof. Dr. Ashraf Tawfik Soliman**, Prof. of Pediatrics, Faculty of Medicine, Alexandria University for giving me the privilege of working under his supervision and for his invaluable help throughout this work and for giving me the idea.

I'm also grateful to **Prof. Dr. Khaled Hussien Taman**, Prof. of Pediatrics, Institute of Postgraduate Childhood Studies, Ain Shams University for his valuable guidance, instructive supervision and generous advice throughout the whole work.

I am also thankful to **Prof. Dr. Mohamed Mustafa Rizk**, Prof. of Clinical Pathology, Faculty of Medicine, Alexandria University, for his good supervision, valuable guidance and great cooperation in the laboratory work.

I am also grateful to **Prof. Dr. Hassan Aly Elkinany**, Prof. of Pediatrics, Faculty of Medicine, Alexandria University for his precious and effective help.

I extend my thanks and gratitude to all members of my family who supported me a lot.

To the spirit of my father I dedicate this work.

LIST OF CONTENTS

	Page
LIST OF ABBREVIATIONS	I
LIST OF FIGURES	III
LIST OF TABLES	VI
INTRODUCTION	1
AIM OF THE STUDY	4
REVIEW OF LITERATURE	5
PATIENTS & METHODS	78
RESULTS	94
DISCUSSION	118
SUMMARY & CONCLUSION	136
RECOMMENDATION	140
REFERENCES	141
APPENDICES	184
ARARIC SUMMARY	

List of abbreviations

ABG Arterial blood gas

ACTH Adrenocorticotrophic hormone

ADH Antiduretic hormone

AI Adrenal insufficiency

ALD Adrenoleukodystrophy

ANS Autonomic nervous system

APS Autoimmune polyglandular syndrome

AVP Argenine vasopressin

3β-HSD 3β-hydroxysterid-dehydrogenase

CBC Complete blood count

CBG | Corticosteroid – binding globulin

CNS Central nervus system

CRH Corticotrophin releasing hormone

CRP C-reactive protein

CSF Cerebrospinal fluid

DHEA Dehydroepiandrosterone

DHEA-S Dehydroepiandrosterone sulphate

DOC Deoxycorticosterone

DXM Dexamethasone

ECF Extracellular fluid

GC Glucocorticoid

GH Growth hormone

GM-CSF Granulocyte monocyte colony – stimulating factor

GR Glucocorticoid receptor

GRE Glucocorticoid receptor element

HDL High density lipoprotein

HDT High dose test

HMG-COA Hydroxyl – methylglutaryl coenzyme A

HPA axis Hypothalamo – pituitary – adrenal axis

HSP Heat shock protein

IFN Interferon

IIH Insulin induced hypoglycemia

IL Interleukin

ITT Insulin tolerance test

LDL Low density lipoprotein

L/S Lecithin / Sphyngomyelin

LDT Low dose test

MR Mineralocorticoid receptor

NK cell Natural killer cell

17-OHCS 17-hydroxycorticosteroids

OMT Overnight metyrapone test

PMN Polymophonuclear

PNMT Phenylalanine -N – methyltransferase

PRA Plasma renin activity

PVN Parvocellular paraventricular nuclei

RANTES Regulated on activation normal T cell expressed and

secreted

RD Respiratory disress

RDS Respiratory distress syndrome

RIA Radioimmunoassay

TGF-β Transferring growth factor β

TLC Total leukocytic count

TNF Tumour necrosis factor

TTN Transient tachypnea of newborn

VIP Vasoactive intestinal peptide

LIST OF FIGURES

Number Page
FIGURE 1: 5
Anatomical relationship between the brain and the pituitary
gland.
FIGURE 2: 7
Nomenclature and targets of hypothalamic release-
controlling hormones and anterior pituitary trophic
hormones.
FIGURE 3: 11
The vasculature and functional interrelationships of the
hypothalamo-hypophyseal complex.
FIGURE 4: 14
Fetoplacental unit.
FIGURE 5: 22
Hormonal steroid biosynthesis.
FIGURE 6: 26
A model of the interaction of asteroid, S and its receptor, R,
and the subsequent events in a target cell.
FIGURE 7: 27
Feedback loops in typical hypothalamo-adrenohypophyseal-
peripheral target cell axis.

Number Page
FIGURE 8: 59
General model for the coordination of the immediate
response to stress.
FIGURE 9: 83
Immulite test unit.
FIGURE 10: 84
Immulite enzyme-amplified luminescence.
FIGURE 11: 100
Basal ACTH (pg/ml) in different groups.
FIGURE 12: 101
Cortisol response to low dose and high dose ACTH
stimulation.
FIGURE 13: 110
Percent increments of cortisol concentrations in normal and
stressed newborns (sepsis and RD).
FIGURE 14: 111
Correlation between cortisol response to low Vs high dose
ACTH test in newborns with sepsis.
FIGURE 15: 112
Correlation between cortisol response to low Vs high dose
ACTH test in newborns with respiratory distress.

Number	Page
FIGURE 16:	113
Correlation between cortisol response to low Vs high	gh dose
ACTH in the control.	
FIGURE 17:	115
Correlation between cortisol response to low dose	Vs high
dose ACTH in the 3 groups.	
FIGURE 18:	115
Correlation between basal cortisol and cortisol resp	onse to
low dose ACTH test in the 3 groups.	
FIGURE 19:	116
Correlation between basal cortisol and peak	cortisol
response to high ACTH dose in the 3 groups.	
FIGURE 20:	117
Correlation between basal cortisol and	ACTH
concentrations in the 3 groups.	

LIST OF TABLES

Number Page
<u>Table 1:</u> 96
Frequency of some clinical presentations of septic newborns
(group I).
Table 2: 97
Frequency of bacteriological findings among septic neonates
(group I).
Table 3: 97
Frequency of etiological causes of RD (Group II).
Table 4: 98
Percent of newborns with different basal and stimulated
cortisol levels in the 3 groups.
Table 5: 99
Basal ACTH levels in septic group Vs control group.
Table 6: 100
Basal ACTH levels in newborns with Rd group Vs control
group.
Table 7: 101
Cortisol levels in septic group Vs control group.

Number	Page
Table 8:	102
Basal ACTH and control levels in septic group wa	ith and
without RD.	
Table 9:	103
Basal ACTH and cortisol levels in septic newborn	ıs with
associated RD in group I and newborns with RD (group	ıp II).
Table 10:	104
Cortisol levels in septic newborns in relation to leu	kocytic
count.	
Table 11:	105
Cortisol levels in septic newborns without meningitis	versus
those with meningitis.	
Table 12:	106
Cortisol levels in septic newborns in relation to morta	lity.
Table 13:	107
Cortisol levels in newborns with RD Vs control.	
Table 14:	108
Basal ACTH and cortisol levels in newborns	s with
pneumonia Vs TTN in group II.	
Table 15:	109
Basal ACTH and cortisol levels in newborns	with
respiratory distress of group II according to RD score.	ı

Number	Page
<u>Table 16:</u>	110
Percent increments in cortisol secretion after low do	se and
high dose ACTH in the 3 groups.	
<u>Table 17:</u>	112
Correlation between different variables in group I (sep	osis).
<u>Table 18:</u>	113
Correlation between different variables in group II (RI	O).
<u>Table 19:</u>	114
Correlation between different variables in group III.	
Table 20:	116
Correlation between different variables in the groups.	

INTRODUCTION

The first month of age is the most critical period in the human life. This neonatal period, being a transition from a totally dependent intrauterine to a totally independent extrauterine life, imposes a significant stressful impact upon the neonate. Numerous physiologic and may be pathologic stressful situations occur by that time, which if not dealt with properly, might jeopardize the outcome (*Rose et al, 1998*).

In the last decade, the understanding of fetal and neonatal hypothalamopituitary adrenal (HPA) axis physiology has revolutionized the management of many conditions of prematurity, septicemia and respiratory distress. Successful adaptation of the newborns to extrauterine life mainly depends on the steroidogenic compartment of the fetal adrenal cortex, its adequate development and production of sufficient endogenous cortisol for perinatal survival towards the end of gestation (*Rose et al, 1998*).

Regulation of fetal HPA axis is a highly complicated process and is under the control of positive and negative feedback circuits, placental hormones and local autocrine / paracrine mediators or growth factors. (Rose et al, 1998) The primary aims of this complex system are to insure appropriate coordination of tissue growth and differentiation, orderly maturation of vital organ systems, and ultimately to act together with the placenta to determine the exact timing of parturition most suitable for transition from intrauterine to extrauterine life. Cortisol is important in maintaining intrauterine homeostasis. It also influences the structural and functional development of a wide variety of fetal tissue, and is essential for the antepartum maturation of organ systems including the lungs,