Medical studies department

Insulin like Growth Factor-1 and Interleukin-6 Levels in serum of Low Birth Weight Infants and in Breast Milk: Relationship to Catch-up Growth

Thesis

Submitted for fulfillment of Ph.D in childhood studies
(Child Health and Nutrition)
Medical Studies Department

By

Maged Atta Fawzy El-Wakeel
M.B.B.Ch/ M.Sc Pediatrics
Cairo University

Supervised by

Prof. Dr. Khaled Hussein Taman
Professor of Pediatrics and
Dean of Institute of Postgraduate
Childhood Studies
Ain Shams University

Prof. Dr. Azza Abdel Shaheed Abdallah
Professor of Child Health
Child Health Department
National Research Centre

Prof. Dr. Karima Abbas Ibrahim
Prof. of Physiology
Medical Physiology Department
National Research Centre

Ain Shams University
2010

Acknowledgment

First and foremost, praise and thanks be to the Almighty (ALLAH) for his limitless help and guidance and peace be upon his prophet.

I would like to express my deepest gratitude to ***Prof. Dr. Khaled Hussein Taman,*** *Professor of Pediatrics and Dean of Institute of Postgraduate Childhood Studies for his great help, valuable guidance, and continuous encouragement through the whole research. I am deeply affected by his care and consideration. I am much honored to have him as my supervisor.*

I wish also to express my sincere and deep appreciations to ***Prof. Dr. Azza Abdel Shaheed Abdallah,*** *Professor of Child Health, National Research Centre for her continuous guidance, support and constructive criticism through the whole work. She has generously devoted much of her time and her effort for planning and supervision of this study.*

And I am also deeply grateful and would like to express my deepest thanks to ***Prof. Dr. Karima Abbas Ibrahim,*** *Prof. of medical Physiology, National Research Centre for her great help and contribution.*

I could not forget the great help of ***Prof. Dr. Gihan Ahmed Fathy,*** *Professor of Child Health, National Research Centre and her precious effort throughout this work.*

Last and not least special thanks are dedicated to all my professors, parents and colleges for their great help during the work

Maged El-Wakeel

CONTENTS

	Page
List of Abbreviation	i
List of Tables	iv
List of Figures	vii
Introduction	1
Aim of the Work	4
Review of Literature	
Chapter 1: Low birth weight	**5**
Chapter 2:	
Growth Patterns of Low birth Weight infants.	**35**
Chapter 3: Insulin Like Growth Factors	**64**
Chapter 4: Cytokines	**82**
Chapter 5:	
Breast milk-borne growth factors and interleukins	**98**
Subjects and Methods	**112**
Results	121
Discussion	160
Summary	175
Conclusion & Recommendations	178
References	181
Arabic summary	أ

List of abbreviations

- ABW: Appropriate birth weight
- ACTH: adrenocorticotropin hormone
- AGA: Appropriate for gestational age
- ALS: Acid labile subunit
- BHSD-2: Beta hydroxy-steroid dehydrogenase-2
- BNF: Brain-derived neurotropic factor
- cAMP: Cyclic adenosine mono-phosphate
- CNTF: ciliary neurotrophic factor
- CPAP: Continuous positive airway pressure
- CPH: carboxypeptidase H
- CSF: Cerebrospinal fluid
- CT-1: cardiotrophin-1
- CTL: cytotoxic T lymphocytes
- DC: dendritic cells
- DNA: Deoxyribonucleic acid
- EGF: Epidermal growth factor
- FGF: Fibroblast growth factor
- GH: Growth hormone
- GIT: Gastro-intestinal tract
- GM-CSF: Granulocyte-Monocyte Colony Stimulating Factor
- GMH: Germinal matrix haemorrhage

- gp l30: glycoprotein 130
- HGF: Hematopoietic growth factor
- IFN: Interferon
- Ig: Immunoglobulin
- IGF-1: Insulin-like growth factor-1
- IGFBP: Insulin-like growth factor binding protein
- IGF-II: Insulin-like growth factor
- IL: Interleukins
- IL6: Interleukins-6
- IUGR: Intrauterine growth retardation
- LBW: Low birth weight
- LC-PUFA: Long chain polyunsa
- LIF: leukemia inhibitory factor
- L-S ratio: Lecithin-sphingomyelin
- MW: Molecular weight
- NBW: Normal birth weight
- NEC: Necrotizing enterocolitis
- NGF: Nerve growth factor
- NMR: Neonatal mortality rate
- NPO: Nothing per oral
- NSILA: non-suppressible insulin-like activities
- NT3: Neurotropin 3
- OSM: oncostatin-M
- PCs: proprotein convertases

- PDGF: Platelet-derived growth factor
- PI-3K: phosphatidylinositol 3-kinase
- PMR: Perinatal mortality rate
- PTHrP: Parathyroid hormone–related protein
- PVL: Periventricular leukomalacia
- RDS: Respiratory distress syndrome
- RNA: Ribo-deoxynucleic acid
- ROP: Retinopathy of prematurity
- SDS: Standard deviation score
- SGA: Small for gestational age
- TGF: Tumor Growth Factor
- TGF-α: Transforming growth factor α
- TGF-β: Transforming growth factor α
- TH: Thyroid hormone
- TNF: Tumor Necrosis Factor
- VLBW: Very low birth weight

List of Tables

Table No.	Titles	Page
(1)	Characteristics and examples of IUGR *	8
(2)	Overview of Risk Factors for Low Birth Weight	10
(3)	Physical maturity scores	16
(4)	Maturity rating	17
(5)	The UNICEF Care Initiative "Care for Women"	33
(6)	Genetic Disorders Characterized by Prenatal Growth Deficiency	44
(7)	Growth factors and fetal growth	49
(8)	Selected immune cytokines and their activities	87
(9)	The Composition of human milk	102
(10)	The Amount and functions of major nutrients in human milk	103
(11)	Major growth factors in human milk and their functions in maternal mammary tissues and the offspring during neonatal development	105
(12)	Immunomodulating agents in human milk	109
(13)	Maternal history of studied group	121
(14)	Descriptive statistics of gestational age and anthropometric data of studied group	125
(15)	Delta changes (Δ changes) of anthropometric data of studied infants.	126
(16)	Catch up growth of studied infants at the 6^{th} month	127
(17)	Descriptive statistics of serum and milk IGF1 and IL6 of studied group	128

(18)	**Delta changes (Δ changes) of serum and milk IGF1 and IL6 in studied infants from enrollment to 6th months**	**130**
(19)	**Sex differences in anthropometric data and gestational age in studied group**	**131**
(20)	**Sex differences in serum IGF-1 and IL-6 in studied group**	**131**
(21)	**Comparison of anthropometric data of studied group in relation to mode of delivery**	**132**
(22)	**Comparison of laboratory data of studied group in relation to mode of delivery**	**133**
(23)	**Comparison of anthropometric data of studied group in relation to appropriateness to gestational age**	**133**
(24)	**Comparison of laboratory data of studied group in relation to appropriateness to gestational age**	**134**
(25)	**Comparison of anthropometric data of studied group in relation to catch up growth**	**135**
(26)	**Comparison of laboratory data of studied group in relation to catch up growth**	**136**
(27)	**Correlation between anthropometric data of the studied group at enrollment in the study and serum IGF-1**	**139**
(28)	**Correlation between anthropometric data of the studied group at 6th month and serum IGF-1**	**141**
(29)	**Correlation between laboratory data of the studied group at enrollment in the study and serum IGF-1**	**143**
(30)	**Correlation between laboratory data of the studied group at 6th month and serum IGF-1**	**144**
(31)	**Correlation between anthropometric data of the studied group at enrollment in the study and serum IL-6**	**146**
(32)	**Correlation between anthropometric data of the studied group at 6th month and serum IL-6**	**148**

(33)	**Correlation between laboratory data of the studied group at enrollment in the study and serum IL-6**	**150**
(34)	**Correlation between laboratory data of the studied group at 6th month and serum IL-6**	**150**
(35)	**Correlation between anthropometric data of the studied group at enrollment in the study and milk IGF-1**	**151**
(36)	**Correlation between anthropometric data of the studied group at 6th month and milk IGF-1**	**153**
(37)	**Correlation between laboratory data of the studied group at enrollment in the study and milk IGF-1**	**155**
(38)	**Correlation between laboratory data of the studied group at 6th month and milk IGF-1**	**155**
(39)	**Correlation between anthropometric data of the studied group at enrollment in the study and milk IL-6**	**156**
(40)	**Correlation between anthropometric data of the studied group at 6th month and milk IL-6**	**156**
(41)	**Correlation between laboratory data of the studied group at enrollment in the study and milk IL-6**	**157**
(42)	**Correlation between laboratory data of the studied group at 6th month and milk IL-6**	**157**
(43)	**Correlation between delta changes of anthropometric parameters and delta changes in serum IGF-1 and IL-6 in studied group**	**158**
(44)	**Correlation between delta changes of anthropometric parameters and delta changes in milk IGF-1 and IL-6 in studied group**	**159**

List of Figures

Figure No.	Titles	Page
(1)	Neuromuscular criteria for maturity	16
(2)	Intrauterine growth curves	38
(3)	Schematic diagram showing the effect of cortisol on the activation of the GH-IGF axis in ovine hepatocytes	49
(4)	Fetal-infant growth chart for preterm infants developed through a meta-analysis of published reference studies	52
(5)	Typical Growth Chart of LBW AGA Infant	54
(6)	Typical Growth Chart of LBW SGA Infant	54
(7)	The GH- IGF- IGFBP axis	65
(8)	Structure of the IGF-1 receptors	67
(9)	The structure of proinsulin and IGFs	69
(10)	Overview of the induction and function of cytokines	83
(11)	IL-6-producing cells and biological activities of IL-6	93
(12)	Maternal risk factors	122
(13)	Mode of delivery in studied group	122
(14)	Consanguinity in studied group	123
(15)	Sex distribution of studied group	123
(16)	Percentage of infants appropriate and small for gestational age in studied groups	124
(17)	Comparison between Length (SDS) at enrollment in the study and length (SDS) at 6th month	126
(18)	Percentage of infants who attained (positive) and those who didn't attain (negative) complete catch up growth at 6th month	127

(19)	**Serum levels of IGF-1 at enrollment in the study and its levels at 6th month**	**128**
(20)	**Serum levels of IL-6 at enrollment in the study and its levels at 6th month**	**129**
(21)	**Milk levels of IGF-1 at enrollment in the study and its levels at 6th month**	**129**
(22)	**Milk levels of IL-6 at enrollment in the study and its levels at 6th month**	**130**
(23)	**Comparison between neonates delivered normally and those delivered by C s in relation to body weight (SDS)**	**132**
(24)	**Comparison between infants who attain and those who didn't attain catch up growth in relation to body weight (SDS) at enrollment in the study**	**135**
(25)	**Comparison between infants who attain and those who didn't attain catch up growth in relation to length (SDS) at enrollment in the study**	**136**
(26)	**Comparison between infants who attain and those who didn't attain catch up growth in relation to Serum IGF-1 at 6th month**	**137**
(27)	**Comparison between infants who attain and those who didn't attain catch up growth in relation to Serum IL-6 at 6th month**	**137**
(28)	**Comparison between infants who attain and those who didn't attain catch up growth in relation to milk level of IGF-1 at enrollment in the study**	**138**
(29)	**Comparison between infants who attain and those who didn't attain catch up growth in relation to milk level of IGF-1 at 6th month**	**138**
(30)	**Correlation between serum IGF-1 and body weight (SDS) at enrollment in the study**	**139**
(31)	**Correlation between serum IGF-1 and length (SDS) at enrollment in the study**	**140**
(32)	**Correlation between serum IGF-1 and head circumference (SDS) at enrollment in the study**	**140**

(33)	**Correlation between serum IGF-1 and body weight (SDS) at the 6th month of age**	**141**
(34)	**Correlation between serum IGF-1 and length (SDS) at the 6th month of age**	**142**
(35)	**Correlation between serum IGF-1 and head circumference (SDS) at the 6th month of age**	**142**
(36)	**Correlation between serum IGF-1 and head circumference (SDS) at the 6th month of age**	**142**
(37)	**Negative correlation between serum IGF-1 and serum IL-6 at enrollment in the study**	**143**
(38)	**Correlation between serum IGF-1 and milk IGF-1 at enrollment in the study**	**144**
(39)	**Negative correlation between serum IGF-1 and serum IL-6 at 6th month of age**	**145**
(40)	**Correlation between serum IGF-1 and milk IGF-1 at 6th month of age**	**145**
(41)	**Negative correlation between serum IL-6 and body weight (SDS) at enrollment in the study**	**146**
(42)	**Negative correlation between serum IL-6 and body length (SDS) at enrollment in the study**	**147**
(43)	**Negative correlation between serum IL-6 and head circumference (SDS) at enrollment in the study**	**147**
(44)	**Negative correlation between serum IL-6 and body weight (SDS) at 6th month of age**	**148**
(45)	**Negative correlation between serum IL-6 and body length (SDS) at 6th month of age**	**149**
(46)	**Negative correlation between serum IL-6 and mid arm circumference (SDS) at 6th month of age**	**149**
(47)	**Correlation between milk levels of IGF-1 and body weight (SDS) at enrollment in the study**	**151**

(48)	**Correlation between milk levels of IGF-1 and head circumference (SDS) at enrollment in the study**	**152**
(49)	**Correlation between milk levels of IGF-1 and skin fold thickness (SDS) at enrollment in the study**	**152**
(50)	**Correlation between milk levels of IGF-1 and body weight (SDS) at 6^{th} month of age**	**153**
(51)	**Correlation between milk levels of IGF-1 and length (SDS) at 6^{th} month of age**	**154**
(52)	**Correlation between milk levels of IGF-1 and head circumference (SDS) at 6^{th} month of age**	**154**
(53)	**Correlation between milk levels of IGF-1 and mid arm circumference (SDS) at 6^{th} month of age**	**154**
(54)	**Correlation between delta changes of serum IGF-1 and delta changes of length (SDS)**	**158**

Introduction

Low birth weight (LBW) is a newborn whose birth weight is less than 2500g ***(Bailey and Byrom, 2006)***. LBW is one of the main predictors of infant mortality. The global incidence of LBW is around 17%, although estimates vary from 19% in the developing countries to 5-7% in the developed countries ***(Valero et al, 2004)***

There are many known risk factors, the most important of which are socio-economic factors, medical risks before or during gestation and maternal lifestyle ***(Herbst et al, 2003)***.

Catch-up growth was considered to be achieved when height, weight, and head circumference (HC) exceed -2SD of reference data and remained above this limit afterwards ***(Brandt et al, 2003)***. The magnitude of catch-up growth during infancy, especially the first 6 months of life, is most critical in decreasing risk at adult shortness ***(Luo and Albertsson, 1998).*** Fetal growth regulatory mechanisms, such as insulin-like growth factor-I and -II, are the primary growth mediators until 6 months of age ***(Karlberg et al, 2002)***

(IGF-1) is a small, single-chain protein that is involved in many aspects of tissue growth and repair. It is similar in size, sequence, and structure to insulin, but has 100-1,000 fold lower

affinity for insulin receptors ***(Mynarcik et al, 1997)***. Although IGF-1 mRNA can be detected in many tissues, the majority of circulating IGF-1 is produced in the liver after stimulation by growth hormone ***(Butt et al, 1999)***

The IGFs are involved in the regulation of growth during pregnancy as well as in early embryonic and fetal development. In most studies, cord blood IGF-1 concentrations correlate with birth weight ***(Bettina et al, 2005)***

Researches have demonstrated that change in total IGF-1 (week 0 to week 3) was a positive predictor of postnatal weight gain, and that a good correlation was found between postnatal weight, length and IGF-1 ***(Lo et al, 2005)***. Also it was found that IGF-1 was significantly high in IUGR infants with catch-up growth with respect to IUGR infants without catch-up growth, indicating its importance in early catch-up growth of IUGR babies ***(Ozkan et al, 1999).***

It has also been shown that IGF-1 is present in breast milk and its concentration is highest prepartum and early postpartum, coinciding with maximal proliferation of mammary cells. It is hypothesized to play a functional role in the growth and development of neonates ***(Elmlinger et al, 2007)***

Interleukins are part of a larger class of polypeptides known as cytokines, these are messenger molecules that transmit signals between various cells of the immune system,