

Accuracy of Interleukin-6 and Interleukin-10 in Prediction of Preterm Birth

Thesis

Submitted for partial fulfillment of the Master Degree
In Obstetrics and Gynecology

Presented by

Omnia Ahmed Hassn Sedeik

M.B.,B.Ch.(2009) Misr University for science and technology
Resident of Obstetrics and Gynaecology, Alexandria Maternity Hospital

Supervised by

Prof. Aly Elyan Khalaf Allah

Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Sherif Fekry Hendawy

Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Sherif Hanafi Hussain

Lecturer of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

**Faculty of Medicine
Ain Shams University**

2014

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

الحمد لله رب العالمين
الذى أنعم علينا بإتمام هذا
العمل



Acknowledgements

*I would like to express my sincere gratitude to **Prof. Aly Elyan Khalaf Allah**, Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University for dedicating so much of his precious time and effort to complete this work. I'm really honored for his continuous support and guidance for me to present this work.*

*I acknowledge with much gratitude to **Dr. Sherif Fekry Hendawy**, Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for his encouragement and help in this work.*

*I can't forget to thank **Dr. Sherif Hanafi Hussain**, Lecturer of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for his great supervision and unlimited help to provide all facilities to accomplish this work.*

✍ **Omnia Ahmed Hassn Sedeik**

Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations.....	i
List of Tables.....	iv
List of Figures.....	v
Protocol.....	
Introduction.....	1
Aim of the Work.....	3
Review of Literature	
Chapter (1): Anatomy of Fetomaternal Interface.....	4
Chapter (2): The Immunology of Successful Pregnancy.....	8
Chapter (3): Epidemiology of Preterm Birth.....	31
Chapter (4): Pathogenesis of Preterm Birth.....	52
Chapter (5): Role of Interleukin-6 and Interleukin-10 in Prediction of Preterm Birth.....	65
Chapter (6): Ritodrine and Inhibition of Acute Preterm Birth.....	87
Patients and Methods.....	96
Results.....	113
Discussion.....	133
Summary and Conclusion.....	144
References.....	147
Arabic Summary.....	

List of Abbreviations

ACOG	: American College of Obstetricians and Gynecologists
ACTH	: adrenocorticotrophic hormone
AUC	: Area under the curve
BMI	: Body mass index
BP	: Blood pressure
BPD	: Bronchopulmonary dysplasia
CCL-2	: Chemokine motif ligand 2
CI	: Confidence interval
CKD	: Chronic kidney disease
CNGOF	: National College of French Gynaecologists and Obstetricians
CP	: Cerebral palsy
CRH	: Corticotropin releasing hormone
CRHBP	: Corticotropin releasing hormone binding protein
CRP	: C reactive protein
CSF	: Colony stimulating factor
CTB	: Cytotrophoplast
CUA	: Complete urine analysis
DAMP	: Damage-associated molecular patterns
DHEA-S	: Dehydroepiandrosterone sulfate
dNK	: Decidual natural killer
E1	: Estrone
E2	: Estradiol
E3	: Estriol
ECM	: Extra cellular matrix
EGF	: Epithelial growth factor
ELBW	: Extreme low birth weight
ELIZA	: Enzyme linked immunosorbent assay
en EVT	: Endovascular extravillous trophoblast
ERα	: Estrogen receptor alpha
ERβ	: Estrogen receptor beta
EVT	: Extravillous trophoblast
FDA	: Food and Drug Administration
GA	: Gestational age
Gai	: G protein alpha inhibitory

List of Abbreviations

GDM	: Gestational diabetes mellitus
GP_{ER}	: G protein-coupled estrogen receptor
GPR30	: G protein-coupled receptor
HCG	: Human chorionic gonadotrophin
HPA	: Hypothalamic-pituitary-adrenal
hPL	: Human placental lactogen
HS	: Highly significant
IAI	: Intra- amniotic infection
iEVTs	: Interstitial extravillous trophoblast
IFN-γ	: Interferon-gamma
IL	: Interleukin
IL-1Ra	: IL-1 receptor antagonist
IQR	: Interquartile range
IUGR	: Intrauterine growth restriction
IVH	: Intraventricular hemorrhage
LBW	: Low birth weight
LIF	: Leukaemia inhibitory factor
LR	: Likelihood ratio
MCP-1	: Monocyte chemotactic protein-1
MMPs	: Matrix metalloproteinases
n/a	: Not applicable
NEC	: Necrotizing enterocolitis
NF-κB	: Nuclear factor kappa B
NO	: Nitric oxide
NPV	: Negative predictive value
NS	: Non significant
OR	: Odds ratio
OXTR	: Oxytocin receptor
PDA	: Patent ductus arteriosus
PE	: Preeclampsia
PGD₂	: Prostaglandin D ₂
PGDH	: Prostaglandin dehydrogenase
PGE₂	: prostaglandin E ₂
PGF_{2α}	: Prostaglandin F ₂ alpha
PPROM	: preterm premature rupture of membranes
PPV	: Positive predictive value

List of Abbreviations

PR-A	: Progesterone receptor A
PR-B	: Progesterone receptor B
PTB	: Preterm birth
PTGS2	: PG endoperoxidase synthase 2
PTHrP	: Parathyroid hormone-related peptide
PTL	: Preterm labour
PTnotL	: Preterm not in labour
RCOG	: Royal. College of Obstetricians and Gynaecologists
RCTs	: Randomised controlled trials
RDS	: Respiratory distress syndrome
RLN	: Relaxin
ROP	: Retinopathy of prematurity
SD	: Standard deviation
SGA	: Small for gestational age
SIDS	: Sudden infant death syndrome
sPL	: Spontaneous preterm labour
STB	: Syncytiotrophoblast
T. vaginalis	: Trichomonas vaginalis
TAT	: Thrombin-antithrombin
TGFB	: Transforming growth factor-b
Th1	: T helper 1
TIMPs	: Tissue inhibitor of metalloproteinase
TL	: Term in labour
TLR	: Toll like receptor
TNF	: Tumour necrosis factor
TnotL	: Term not in labour
VLBW	: Very low birth weight
VSMCs	: Vascular smooth muscle cells
WBC	: White blood cell

List of Tables

Table No.	Title	Page No.
Table (1):	Demographic data of studied women	113
Table (2):	Initial cervical examination in included women.....	116
Table (3):	Serum IL-10 and IL-6 concentrations in included women.....	118
Table (4):	Latency interval and timing of delivery in included women.....	119
Table (5):	Difference between women who delivered within 7 days and women who delivered after 7 days regarding demographic data.....	121
Table (6):	Difference between women who delivered within 7 days and women who delivered after 7 days regarding cervical examination on admission	124
Table (7):	Difference between women who delivered within 7 days and women who delivered after 7 days regarding serum IL-10 and IL-6 concentrations	126
Table (8):	Correlation between latency interval and measured variables.....	128
Table (9):	Correlation between each of serum IL-10 and IL-6 concentrations and measured variables	129
Table (10):	Areas under the Receiver Operator Characteristics (ROC) curves for serum IL-10 and IL-6 concentrations as predictors of delivery within 7 days	131
Table (11):	Accuracy of serum IL-10 and IL-6 concentrations as predictors of delivery within 7 days	132

List of Figures

Figure No.	Title	Page No.
Figure (1):	Key processes in decidualization, implantation and pacental development.....	5
Figure (2):	Cellular interactions involved in decidual spiral artery remodelling	11
Figure (3):	Mechanical stretch and subsequent leukocyte infiltration are essential for onset of labour	28
Figure (4):	Biochemical cascades involved with preterm labour	60
Figure (5):	Bar-chart showing age distribution in included women	114
Figure (6):	Bar-chart showing BMI distribution in included women	114
Figure (7):	Pie-chart showing parity distribution in included women	115
Figure (8):	Pie-chart showing gestational age distribution in included women.....	115
Figure (9):	Pie-chart showing initial cervical dilation in included women	117
Figure (10):	Pie-chart showing initial cervical effacement in included women	117
Figure (11):	Box-Plot chart showing serum IL-10 and IL-6 concentrations in included women.....	118
Figure (12):	Box-Plot chart showing latency interval in included women	119
Figure (13):	Pie-chart showing latency interval in included women	120

List of Figures

Figure No.	Title	Page No.
Figure (14):	Box-Plot chart showing difference between women who delivered within 7 days and women who delivered after 7 days regarding BMI.....	122
Figure (15):	Box-Plot chart showing difference between women who delivered within 7 days and women who delivered after 7 days regarding gestational age.....	122
Figure (16):	Box-Plot chart showing no difference between women who delivered within 7 days and women who delivered after 7 days regarding age.....	123
Figure (17):	Box-Plot chart showing no difference between women who delivered within 7 days and women who delivered after 7 days regarding parity	123
Figure (18):	Bar-chart showing difference between women who delivered within 7 days and women who delivered after 7 days regarding cervical dilatation on admission	125
Figure (19):	Bar-chart showing difference between women who delivered within 7 days and women who delivered after 7 days regarding cervical effacement on admission.....	125
Figure (20):	Box-Plot chart showing difference between women who delivered within 7 days and women who delivered after 7 days regarding serum IL-10 concentration.....	127

List of Figures

Figure No.	Title	Page No.
Figure (21):	Box-Plot chart showing difference between women who delivered within 7 days and women who delivered after 7 days regarding serum IL-6 concentrations	127
Figure (22):	Scatter-Plot showing correlation between each of serum IL-10 and latency interval.....	130
Figure (23):	Scatter-Plot showing correlation between each of serum IL-6 and Latency Interval	130
Figure (24):	ROC curves for serum IL-10 and IL-6 concentrations as predictors of delivery within 7 days	131

Introduction

Preterm birth is defined as birth prior to 37 completed weeks of gestation (*Beck et al., 2010*), while term is 40 weeks. Fifteen million neonates, about 11% of the world's births, are born preterm every year (*Melville and Moss, 2013*). The incidence of preterm birth is as high as 11.9 % in Africa, 10.6% in North America, while 6.2% in Europe (*Beck et al., 2010*).

Preterm birth accounts for 35% of all neonatal deaths worldwide: over one million every year (*Melville and Moss, 2013*). Survivors of preterm birth face lifelong morbidity, with increased risks of cerebral palsy, intellectual disability (*Mwaniki et al., 2012*), respiratory disease (*Jobe et al., 2008*) and vision impairment (*O'Connor et al., 2007*). Preterm infants are at high risk of acquiring infections, and this is a significant contributor to mortality in this group. The infection related neonatal deaths may be due to their immature immune systems (*Wynn et al., 2009*). Preterm infants have deficiencies in both innate and adaptive immunity, and in the interaction between these two systems (*Strunk et al., 2011*).

The etiology of preterm labour is multifactorial and as such, the underlying cause of preterm labour is often unknown. There is a strong association between preterm labour, infection and inflammation, and research in this field has dramatically increased over the last few decades (*Sykes et al., 2011*).

During pregnancy, the balance between the proinflammatory T-helper1 (Th1) cytokines and the anti-inflammatory T- helper2 (Th2) cytokines undergoes a shift resulting in a predominance of Th2, as interleukin-10 (IL-10) is a specific Th2 cytokine that serves as a protective factor for preterm birth (*Lyon et al., 2010*).

Investigators believe that the protective effects of IL-10 are similar to the effects of progesterone (*Chaouat et al., 1995*). In contrast, interleukin-1 (IL-1) and interleukin-6 (IL-6) are specific Th1 cytokines associated with an increased risk of preterm birth (*Challis et al., 2009*).

Aim of the Work

The aim of this work is to measure the accuracy of interleukin 6 (IL6) and interleukin 10 (IL10) in prediction of preterm birth (PTB).

Anatomy of Fetomaternal Interface

The placenta serves as the interface between the fetal and maternal environments as it is composed of both maternal and embryonic blood vessels. From the fetal side, two arteries and one vein from the umbilical cord feed into the placenta where they further branch in the chorionic villi forming capillary loop. On the maternal side, the extravillous cytotrophoblasts (EVTs) are involved in remodeling of the maternal spiral arteries, which lead to the increased blood flow toward the fetomaternal interface (*Cartwright et al., 2010*).

The placenta is involved in the exchange of gases, nutrients and waste products between the mother and the growing fetus. Moreover, the placenta functions as an endocrine organ producing a number of pregnancy-associated hormones and growth factors to regulate fetal growth and maternal physiology. Finally, placenta acts as a barrier to protect the fetus from maternal immune attack(*Fu et al., 2013*).

The proper placental development is vital for embryo survival and health, as defects in the function and development of the placenta have been associated with many complications, such as preterm labour PTL, preeclampsia (PE),intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) and gestational diabetes mellitus(GDM) (*Lee et al., 2011*).