Interleukin -6 Gene polymorphism and its relation to spontaneous preterm labor

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In Obstetrics and Gynecology

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بسم الله الرحمن الرحيم

" قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلا مَا
عَلَّمْتَنَا إِنَّكَ أَنْتَ العَلِيمُ الحَكِيمُ "

صدق الله العظيم

(البقرة – الآية ٣٢)

Abstract

This study was done to establish the relationship between Il-6 promoter -174 polymorphism and spontaneous preterm birth more than 28 weeks and less than 37 weeks among Egyptian women.

The study was conducted at the labour ward of Kasr Al Ainy hospital during the period from October 2011 to May 2012.

The population of this study comprised women presenting to the labour ward and outpatient clinic of Kasr Al Ainy hospital 180 pregnant women were selected. The idea of the study was explained to the women who were included as a study group and their informed consent was obtained before inclusion in this study.

Key Words:

The Epidemiology of Preterm Labour and Delivery, Interleukins: Biological Properties and Therapeutic Potential, Current Understanding of Genetic Factors in Preterm Birth

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Mahmoud El-Alfy

M.B.,B.Ch.

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LIST OF ABBREVATIONS

AA	Avachidonis Acid
AF	Amniotic fluid
AFI	Amniotic fluid index
AFP	Alpha feto-protein
BMI	Body mass index
BV	Bacterial vaginosis
BV	Bacterial Vaginosis
C.S	Cesarian Section
C.trachomatis	Chlamydia trachomatis
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
COX	Cyclooxygenase
CREB	Camp response element binding prote
CRH	Corticobrophin releasing horm
CRP	C-reactive protein
CS	Cesarean section
CTG	Cardiotocography
DBD	DNA binding domain
DD	Differential diagnosis
DDT	Dichlorodiphenyltrichloroethane
DES	Diethyl Stilbestrol
DNA	Deoxyribonucleic acid
fFN	Fetal fibronectin
GBS	group B streptococcus
HBD	Hormone binding domain
HCG	Human chorionic gonadotrophin
HLOD	Heterogoneity logarithm of odds
IBS	Identical by state
IFNG	Interferon gamma
IGF-1R	Insulin Like Growth Factor Receptor 1
IGFBP-1	Insulin-like growth factor binding protein-1
IL	Interleukin

IL-1B	Interleukin-1 B
IQR	Interquartile range
IUGR	Intra uteiine grouth Resbriction
LEEP	loop electrosurgical excision procedures
LPS	Lipopolysaccharide
LPS	Lipo poly sccharide
MOI	Mode of inheritance
NF-KB	Nuclear Factor Kappa B
NST	non-stress test
OR	Odds ratio
P	Probability
P&E	Dilatation & Evacuation
PG D2	Prostaglandin D2
PG DH	15 Hydroxy Prostaglandin dehydrogenase
PG E2	Prostaglandin E2
PG F2a	Prostaglandin F2a
PG H2	Prostaglandin H2
PG I2	Prostaglandin I2
PGE2	Prostaglandin E2
PGF2 alpha	Prostaglandin F2 alpha
PGS	Prostaglandins
PKC	Protein kinase C
PL	Phospholipase
PPRES	Pevoxisome proliferator response elements
PPROM	preterm PROM
PRA	Progesterone receptor A
PROM	Premature rupture of the fetal membranes
PTB	Preterm Birth
PTD	Preterm delivery
PTL	Pre term labour
PTL	Preterm labor
RDS	Respiratory distress syndrome
ROM	Rupture of membranes

RRR	Relative risk Ratio
RT-PCR	Reverse transcriptase PCR
SD	Standard deviation
SLE	Systemic lupus erythematosus
STD	sexually transmitted disease
T. vaginalis	Trichomonas vaginalis
TNF alpha	Tumour necrosis alpha
TNFA	Tumor recrosis factor
TPROM	term PROM
TX	Thromboxane
vAF	vaginal amniotic fluid

Introduction

Preterm birth is the leading cause of neonatal morality and a substantial portion of all birth related morbidity. Preterm delivery accounts for 56% of neonatal deaths and 50% of neurological disability in childhood. Prematurity rates have not changed in recent decades. ***(Shenan 2003).***

A preterm delivery as defined by the world health organization is one that occurs at less than 37 and more than 20 weeks gestational age. In the United States, the preterm delivery rate is approximately 11%, whereas in Europe it varies between 5% and 7%. In spite of the advances in obstetric care, the rate of prematurity has not decreased over the past 40 years. ***(Goldenberg 2002).***

Preterm labor is multifactorial, it is associated with preterm rupture of membranes, cervical incompetence, polyhydramnios, fetal and uterine anomalies, social factors, stress, smoking and heavy work and genetic predisposition. ***(Haram et. Al., 2003).***

Neonatal morbidity rates have decline in the recent years largely because of improved neonatal intensive care and better access to these services. With appropriate medical care, neonatal survival dramatically improves as gestational age progress. ***(Tan et. Al., 2006).***

Several methods were tried to predict patient at higher risk of developing preterm labor. A short cervix identified on vaginal ultrasound has a good predictive value for early deliver, even in a low risk group and a cervical length of less than 15 mm. will result in a 50% chance of delivery before 32 weeks' gestation. The predictive value in multiple pregnancies is similar. Identifying fetal fibronectin in vaginal secretions after 22 weeks gestation also has a strong association with preterm delivery Both these tests perform far better than previous history as predictors of preterm delivery, which has traditionally been the way to identify a group at risk, as most women with recurrent prematurity will achieve a term pregnancy in their subsequent pregnancy. Although it is impractical to screen all women, populations at risk

could be targeted with these tests to identify groups for intervention. .***(Shenan 2003).***

Proper management of threatened preterm labor significantly reduces neonatal morbidity and mortality. The therapeutic interventions in the setting of preterm labor aim to inhibit or reduce the strength and frequency of contractions, which delays the time of delivery, and to optimize fetal status before preterm delivery. ***(Tan et al 2006).***

Therapeutic interventions usually include be rest, hydration, tocolysis and corticosteroid administration. ***(Iams et al 2002).***

Preterm Birth is responsible for nearly 75% of perinatal mortality and approximately half of cases of long term neuologic morbidity. The most serious sequelae of prematurity and highest risk of death occur in those neonates born at less than 32 weeks' gestation.

With the dramatic advances in molecular genetics in the past decade, have lead to increasing speculation that variations in the maternal immune response (mediated by genetic variation in the inflammatory response) might be integrally involved in the pathophysiology of spontaneous preterm labor and preterm birth. ***(Porter et al., 1997).***

Many SNPs most commonly associated with spontaneous preterm labor and preterm birth are the polymorphisms at the IL-1β Exon 5 + 3954, and TNF-α-308 Loci and IL-6 polymorphism. ***(Genc et al., 2002).***

Simhan et al. reported the association of a polymorphism at the – 174 position in the promoter region of the IL-6 gene with a decreased risk of preterm birth in a cohort of primarily Caucasian women. ***(Simhan et al 2003).***

Interleukin 6 (IL-6) is critical cytokine in the cascade of host response to infection IL-6 activates the acute phase response, stimulates T lymphocytes, induces the terminal differentiation of B lymphocytes, and induces C reactive protein production. In the setting of intrauterine infection and preterm labor, the amniotic fluid concentration of Il-6 is increased in excess of that of other proinflammatory products. Increase in IL-6 concentration are seen in

maternal serum, cervix, and amniotic fluid in preterm labor. In large part, the production of IL-6 is under genetic regulation.

Polymorphisms have been described for many human cytokine genes. These polymorphisms represent normal allelic variation, frequently within the regulatory region of cytokine genes. Specific polymorphisms are associated with increased susceptibility to certain in factious diseases and increased severity of autoimmune disease. A polymorphism in the promoter region of IL-6 on chromosome 7 is associated with production of IL-6.

Aim of the Work

To establish the relationship between Il-6 promoter -174 polymorphism and spontaneous preterm birth more than 28 weeks and less than 37 weeks among Egyptian women .