THE ASSOCIATION BETWEEN PENTRAXIN 3 IN MATERNAL CIRCULATION AND INTRAUTERINE GROWTH RESTRICTION: A CASE CONTROL STUDY

Thesis

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LIST OF ABBREVIATIONS

Abbreviations	Full term
a.umbilicalis	Arteria umbilicalis
a.uterinae	Arteriae uterinae
AC	Abdominal circumference
AFI	Amniotic fluid index;
AMI	Acute myocardial infarction
AUC	Area under the curve
BMI	Body mass index
BPD	Biparietal diameter
CI	Confidence Interval
COC	Cumulus oophorus cells in ovary
CRP	C-reactive protein
CS	Caesarean section
DCs	Dendritic cells
ECM	Extracellular matrix
ECs	Endothelial cells
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FGR	Fetal growth restriction
FL	Femur length
GA	Gestational age
HIV	Human immunodeficiency virus
IUFGR	Intrauterine fetal growth restriction
IUGR	Intrauterine growth restriction
LPS	Lipopolysaccharide
MDL	Minimum detectable limit
NK	Natural killer
NPTXI	Pentraxin I
NPTXII	Pentraxin II
NSCLC	Non-small cell lung cancer
OMPs	Outer membrane proteins
OR	Odds ratio
PCR	*Polymerase chain reaction*
PI	Pulsatility index
PMNs	Polymorphonuclear cells
PTX3	Pentraxin 3

RI ..... Resistance index
ROC ..... Receiver-operating characteristic curve
RT-PCR..... Reverse transcriptase polymerase chain reaction
S/D ratio ..... Systolic to diastolic ratio
SAP ..... Serum amyloid P-component
SCLC ..... Small cell lung cancer
SDS-PAGE..... Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SGA ..... Small for gestational age
TGF-α ..... Tissue growth factor-alpha
TIMPs ..... Trophoblasts and their inhibitors
TLR..... Toll-like receptor
TNF-α..... Tumor necrosis factor-α
TSG-14..... TNF-stimulated gene
UA-RI ..... Umbilical artery resistance index
UA-RI..... Umbilical artery resistance index
US..... Ultrasound.
VEGF ..... Vascular Endothelial Growth Factor

INTRODUCTION

The term, small for gestational age (SGA) fetus, describes that fetus with growth parameters below the 10th percentile. This term cannot differentiate between physiological and pathological smallness, distinction necessitates the assessment of the fetal growth potential**.** Intrauterine growth restriction (IUGR) describes the fetus who failed to reach its growth potential because of genetic and/or environmental causes. This term is not designated to describe a constitutionally small, but otherwise healthy fetus[1]. It is essential to differentiate between a SGA fetus and a fetus with IUGR, as the latter is at risk for serious short and long term consequences while the earlier is not at high risk of perinatal mortality or morbidity if it is simply small because of constitutional elements[2].

Pentraxin 3 (PTX3) is a well-known long pentraxin produced by many cells (epithelial cells, endothelial cells, fibroblasts, monocytes, polymorphonucelar leucocytes, macrophages, and dendritic cells)[3,4]; it plays an essential role in female fertility, innate immunity, and inflammation. Recently, the role of PTX3 has been investigated in normal pregnancy, preeclampsia, intrauterine growth restriction, preterm labor, premature rupture of fetal membranes;

intraamniotic inflammation, recurrent miscarriage and implantation disorders[5,6].

Antenatal diagnose of placental IUGR is challenging, the presence of an easily accessible marker in the maternal circulation, would help to classify SGA foetuses into high and low risk groups. Women with IUGR have increased PTX3levels associated with altered placentation; however, this finding warrants further investigation[7]. The aim of the current study was to compare the circulating PTX3 levels in pregnant women with and without IUGR.

AIM OF THE WORK

The aim of this study is to show the association between maternal circulating PTX3 level in normal pregnant women and those with IUGR.

Chapter One

INTRAUTERINE GROWTH RETARDATION

Distinguishing the constitutionally small fetus from the growth restricted fetus is a complex diagnostic and management problem, but is important. A constitutionally small fetus achieves its normal growth potential and has a good prognosis whereas the fetus whose growth potential is restricted is at increased risk of perinatal morbidity and mortality[1]. Fetal growth restriction (FGR) that results from intrinsic fetal factors such as aneuploidy, congenital malformations, and fetal infection carries a guarded prognosis that often cannot be improved by any intervention. FGR related to uteroplacental insufficiency has a better prognosis, but is still associated with an increased risk of adverse outcome[4].

The common definition of intrauterine growth retardation (IUGR) is a birth weight under the 10^{th} Percentile.

Most authorities prefer to maintain the strict and more inclusive definition of IUGR as birth weight less than 10 percent of predicted fetal weight for gestational age. Using the 10^{th} percentile as a standard result in overdiagnosis of IUGR. Other authors, however, have suggested using the 5th percentile to define IUGR infants[2]. The counter argument in favor of a strict definition is that birth weight is probably the

single most important factor affecting neonatal morbidity and mortality and should be aggressively screened for. A lack of consensus among perinatologists makes it difficult to fully define the extent of IUGR and the subsequent effectiveness of interventions[2].

1.1 Etiology:

Table (1): Condition Associated with Intrauterine Growth Retardation

Medical	Maternal	Infectious	Congenital
Chronic hypertension	Smoking	Syphilis	Trisomy 21
Preeclampsia early in gestation	Alcohol use	cytomegalovirus	Trisomy 18
Diabetes mellitus	Cocaine use	Toxoplasmosis Rubella	Trisomy 13
Systemic lupus erythermatosus	Warfarin (Coumadin,Panwarfin)	Hepatitis B	Turner's syndrome
Chronic renal disease	Prior history of pregnancy with intrauterine growth retardation	HSV-1 orHSV-2	
Inflamatory bowel disease	Resting at altitude above 5,000 feet		
Severe hypoxic lung disease			

HSV = Herpes simplex virus, **HIV**= Human immunodeficiency virus.
Information from references 1 and 3

Historically, IUGR has been categorized as symmetric or asymmetric. Symmetric IUGR refers to fetuses with equally poor growth velocity of the head, the

abdomen and the long bones. Asymmetric IUGR refers to infants whose head and long bones are spared compared with their abdomen and viscera. It is now believed that most IUGR is a continuum from asymmetry (early stages) to symmetry (late stages)[6].

Maternal causes of IUGR account for most uteroplacental cases. Chronic hypertension is the most common cause of IUGR. Moreover, the infants of hypertensive mothers have a three-fold increase in perinatal mortality compared with infants with IUGR who are born of normotensive mothers. Because of their significant risk, one author recommends delivering these infants by 37 weeks of gestational age[4].

Preeclampsia causes placental damage that results in uteroplacental insufficiency. The pathogenic mechanism is thought to be a failure of trophoblastic invasion by maternal spiral arterioles by 20 to 22 weeks of gestation. This failure causes luminal narrowing and medial degeneration, leading to diminished blood flow to the developing infant. Consequently, these infants fail to grow normally[5].

Infectious causes of fetal growth delay account for about 10 percent of all cases of IUGR. These causes include the "TORCH" group: Toxoplasma gondii, rubella, cytomegalovirus and herpes simplex virus types 1 and 2.