Assessment of Decidual Natural Killer Cells CD56^{+} Population in Placental Bed in Fetal Growth Restriction

Thesis

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Noha Mahmoud Kasim

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List of Abbreviations

AC	**:**	Abdominal circumference
ACA	**:**	Anticardiolipin antibodies
ACOG	**:**	American Congress of Obstetricians and Gynecologists
AFI	**:**	Amniotic fluid index
AIUM	**:**	American Institute of Ultrasound in Medicine)
Ang	**:**	Angiopoietin
APS	**:**	Antiphospholipid syndrome
ART	**:**	Artificial reproductive techniques
BPD	**:**	Biparietal diameter
BPP	**:**	Biophysical profile
CMV	**:**	Cytomegalovirus
COPD	**:**	Chronic Obstructive Pulmonary Disease
CRL	**:**	Crown-rump length
CTG	**:**	Cardiotocography
CXC R3	**:**	Chemokine receptor R3
CXCR1	**:**	Chemokine receptor R1
DCs	**:**	Dendritic cells
DNA	**:**	Deoxyribonucleic acid
dNK	**:**	Decidual Natural killer cells
ECM	**:**	Extracellular matrix
EFW	**:**	Estimated fetal weight
EFW	**:**	Estimated fetal weight
eNK	**:**	Endometrial Natural killer cells
EVT	**:**	Extravillous **trophoblast**
FcγRIII	**:**	Fragment crystallizable

FHR	**:**	Fetal heart rate
FL	**:**	Femur length
GM-CSF	**:**	Granulocyte–macrophage colony-stimulating
GRIT	**:**	*The Growth Restriction Intervention Trial*
HC	**:**	Head circumference
HIV	**:**	Human immunodeficiency virus
HLA	**:**	Human leukocyte antigen
HPF	**:**	High Power Field
IFNγ	**:**	Interferon-γ
IG	**:**	Immunoglobulin
IL-2Rβ	**:**	Interleukin-2 receptor subunit beta
IL-3	**:**	Interleukin-**3** receptor
IL-8	**:**	Interleukin-8 receptor
IL-IRI	**:**	Interleukin-iri
IP-10	**:**	Inducible protein 10
IQ	**:**	Intelligence quotient
IUGR	**:**	Intrauterine growth restriction
IVF	**:**	In vitro fertilization
LBW	**:**	Low birth weight
MCA	**:**	Middle cerebral artery
Mhc	**:**	Major histocompatibility complex
Nk	**:**	Natural killer T cells
NKT	**:**	Natural killer cells
NO	**:**	Nitric oxide
PGF	**:**	Placental growth factor
PGs	**:**	Prostaglandins
PIGF	**:**	Phosphatidylinositol-glycan biosynthesis class F

		protein
PlGF	**:**	Placental growth factor
RBC	**:**	Red blood cell
RCOG	**:**	Royal College of Obstetricians and Gynecologists
'SFH'	**:**	Symphysis fundal hieght
sFlt1	**:**	Soluble fms-like tyrosine kinase-1
sFlt-1	**:**	Soluble fms-like tyrosine kinase receptor-1
SGA	**:**	Small for gestational age
SLE	**:**	Systemic lupus erythematosus
TB	**:**	Tuberculosis
TCR	**:**	T-cell receptor
TGF- β	**:**	Transforming growth factor **beta** 1
Th type-1	**:**	T helper cells type-1
Th2	**:**	Type-2 T-helper
TNF-α	**:**	Tumour necrosis factor-α
TORCH	**:**	Toxoplasmosis, rubella, cytomegalovirus, herpes simplex
UA	**:**	Umbilical artery
VEGF	**:**	Vascular endothelial growth factor

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Introduction

Several definitions and terminology has been used to define IUGR, including but not limited to estimated fetal weight <25 %, <15 %, <10 %, <5 %, <3 %, <2.5 %, and <1 % for gestational age. Other definitions of IUGR include estimated weight less than 2 standard deviations below the mean weight for gestational age ***(Suhag and Berghella, 2013).***

The causes of IUGR are broadly described under three main categories: maternal, fetal, and placental ***(Hendrix and Berghell, 2008).***

Normal fetal growth reflects the interaction between the genetically predetermined growth potential and the presence of a healthy fetus, placenta and mother ***(Nardozza et al., 2017)***.

A Several maternal demographic factors have been associated with IUGR. Women at extremes of reproductive age, especially young maternal age, are at increased risk for IUGR. There no association between maternal age and low birth weight and reported an independent effect of social factors, such as ethnicity, poverty status, age at menarche, maternal height, net maternal weight gain, and smoking during pregnancy, on birth weight in adolescent mothers ***(Suhag and Berghella, 2013).***

Fetal factors can vary from genetic causes, congenital malformations, fetal infection, or other causes, including multiple pregnancies. Genetic causes can contribute to 5-20 % of IUGR, especially for early onset growth restricted fetuses. Genetic causes further include various abnormalities, such as chromosomal abnormalities, e.g., trisomy 21, 18, 13, and 16. Of these, trisomy 18 is associated with more severe IUGR compared with trisomy 21 or 13. Trisomy 16 is known to be a lethal chromosomal abnormality in the non-mosaic state; however, in the presence of placenta mosaicism, trisomy 16 can result in IUGR ***(Baschat et al., 2012).***

Placental insufficiency accounts for many cases of IUGR and can affect up to 3 % or more of all pregnancies. The pathogenesis of IUGR is not well defined; defects in the placental circulation and transport can affect the nutrient transport to the fetus, resulting in IUGR. The relative decrease in placental mass and function can result in the development of IUGR. Several animal models have shown that fetal growth can be impaired when up to 50 % of the placental mass is removed. Like the animal model, growth-restricted human fetuses are noted to have approximately a 24 % smaller placental weight compared with a normally grown fetus ***(Brett et al., 2014).***

The asymmetrical IUGR fetuses are noted to be at higher risk for major anomalies, low birth weight, perinatal

mortality, preterm delivery, cesarean section, and overall poor outcomes, compared to symmetrical IUGR ***(Dashe et al., 2000).*** Umbilical artery Doppler studies and antenatal surveillance are very good predictors of pregnancy outcomes in all types of IUGR ***(Alfirevic and Gyte, 2010).***

Perinatal morbidity and mortality is significantly increased in the presence of birth weight less than 10th percentile. After prematurity, IUGR is the second leading cause of perinatal mortality. IUGR fetuses have approximately a fivefold to tenfold increased risk of dying in utero, with up to 23 % to 65 % of stillbirths ***(Chen et al., 2011).***

The first step in diagnosis of fetus with growth restriction is to establish accurate dating. There are several formulae to date the pregnancy from early biometrics, with low systematic and random errors. Crown-rump length (CRL) is a biometric parameter that can be measured in the early stages of gestation. Technically the main limitation is the progressive bending of the embryo which makes measurements less reliable beyond 12-13 weeks of gestation (or 60-70 mm).If possible, below the 14 weeks, all obstetric ultrasound units are currently recommended to adopt this method of assessing gestational age from crown rump length. From then on, it seems conceptually more appropriate to use cephalic (head circumference) and/ or femur (femur length) biometrics ***(Xu et al., 2015).***