Vascular Endothelial Growth Factor In Neonates With Intrauterine Growth Restriction

Thesis

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List of Abbreviations

ABG	:	Arterial blood gas
AC	:	Abdominal circumference
AFI	:	Amniotic fluid index
AGA	:	Appropriate for gestational age.
AUC	:	Area under curve.
CAD	:	Coronary artery disease
CBC	:	Complete blood count.
CI	:	Confidence interval
CMV	:	Cytomegalo virus
CNS	:	Central nervous system
CRP	:	C-Reactive protein.
CVS	:	Cardiovascular system
DV	:	Ductus Venosus
EC	:	Endothelial cells
EFW	:	Estimated fetal weight
FGR	:	Fetal growth restriction
Hb	:	Hemoglobin.
HC	:	Head circumference.
Hct	:	Hematocrit.
HF	:	Hypotensive factor
HIF	:	Hypoxia inducible factor
HSC	:	Hematopoietic stem cells
IUGR	:	Intrauterine growth restriction
IVC	:	Inferior vena cava
LBW	:	Low birth weight.
LMP	:	Last menstrual period
LSECs	:	Liver sinusoidal endothelial cells
MCA	:	Middle cerebral artery
MRI	:	Magnetic resonant imaging
mRNA	:	Messenger ribonucleic acid
MVP	:	Maximum vertical pocket
NICU	:	Neonatal intensive care unit.
NPV	:	Negative predictive value.
NRP	:	Neuroplin

List of Abbreviations (Cont.)

PAD	:	Periphral artery disease
PET	:	Partial exchange transfusion
PI	:	Pulsatility Index
PLGF	:	Placental growth factor
PLT	:	Platelet.
PO_2	:	Oxygen pressure
PPV	:	Positive predictive value.
PSV	:	Peak systolic velocity
PT	:	Preterm.
RI	:	Resistance index
ROP	:	Retinopathy of prematurity
SCG	:	Superior cervical ganglia
SD	:	Standard deviation.
SGA	:	Small for gestational age
svVEGF	:	Snake venom vascular endothelial growth factor
U/S	:	Ultrasound.
UA	:	Umbilical artery
VEGF	:	Vascular endothelial growth factor
VEGFR	:	Vascular endothelial growth factor receptor
VPF	:	Vascular permeability factor
WBCs	:	White blood cells.

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Introduction

Intrauterine growth restriction (IUGR, also called fetal growth restriction [FGR]) is the term used to designate a fetus that has not reached its growth potential because of genetic or environmental factors. This term should not be used to describe a constitutionally small, but otherwise healthy fetus **(Divon and Ferber, 2011).**

IUGR is often classified as reduced growth that is symmetric or asymmetric. Symmetric IUGR often has an earlier onset with equal affection of head circumference, weight and length. Asymmetric IUGR is often of late onset with relative head growth sparing **(Tsatsaris et al., 2003)**.

Angiogenesis, a critical process for growth and development, is altered in intrauterine growth retardation (IUGR). Vascular endothelial growth factor (VEGF) is essential for both physiological and pathological angiogenesis **(Boutsikou et al., 2005)**.

Oxygen is thought of be a major regulator of VEGF function, as VEGF and its receptor are up regulated by low oxygen pressure (Po_2) **(Ariadne et al., 2005)**.

Aim of the study

The aim of this study is to investigate the relation between the level of vascular endothelial growth factor (VEGF) and intrauterine growth restriction (IUGR) as a marker of low O_2 tension.

Vascular Endothelial Growth Factor

Introduction:

Vascular Endothelial Growth Factor (VEGF) is involved in protein synthesis. They are important for vasculogenesis (De novo formation of blood vessels of the embryonic vascular system) and angiogenesis (Formation of blood vessels from pre-exiting vasculature) **(Morimoto et al., 2007).**

VEGF was originally defined as a tumor cell derived from Vascular Permeability Factor **(Connolly et al., 1989**). VEGF is also known as Vascular Permeability Factor (VPF) or Vasculotropin. It is a highly specific endothelial cell mitogen which promotes angiogenesis and has potent vascular permeability that enhances inflammatory properties (**Vasile et al., 2001**).

Types of VEGF

VEGF consists of seven members [VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F (snake venom VEGF svVEGF) and Placental Growth Factor (PGF)]. All have the same structure of (8 spaced cysteine residues) in the VEGF domain but differ in their biological and physical activities. **(Roy et al., 2006).**

1- Vascular Endothelial Growth Factor-VEGF-A:

Referred to as VEGF and also known as Vascular Permeability Factor (VPF), it is the key molecule of angiogenesis and vasculogenesis (proliferation, sprouting,

migration and tube formation of endothelial cells**) (Ferrara et al., 2003).**

Its gene is located at chromosome 6p21.3.VEGF-A acts on the following receptors: Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1), Vascular Endothelial Growth Factor Receptor-2(VEGFR-2),Neuroplins-1 (NRP-1) and Neuroplins-2 (NRP-2**) (Klagsburn et al., 2002).**

Its action on VEGFR-1 mediates its role in pathological conditions while its action on VEGFR-2 mediates its role endothelial cell growth **(Takahashi & Shibuya,2005).**

It has 6 isoforms VEGF-A121, VEGF-A145, VEGF-A148,VEGF-A162,VEGF-A165,VEGF-A165b,VEGF-A183, VEGF-A189 & VEGF-A206 **(Lange et al.,2003).** These isoforms has distinct but overlapping functions **(Roy et al., 2006).**

2- Vascular Endothelial Growth Factor-B (VEGF-B):

Its gene is located on chromosome11q13. VEGF-B acts on VEGFR-1 & NRP-1. **(Roy et al., 2006).**

It has 2 isoformsVEGF-B167 and VEGF-B186 **(Takahashi & Shibuya, 2005).**

It has a role in vascular remodeling in cases of inflammatory arthritis and protection of brain from ischemia **(Sun et al., 2004).**

3- Vascular Endothelial Growth Factor-C (VEGF-C):

Its gene located on chromosome 4q34**.**VEGF-C acts on VEGFR-2, VEGFR-3 **(Roy et al.,2006).**

It has a role in lymphanogenesis **(Karkkainen et al., 2004).**

4- Vascular Endothelial Growth Factor-D (VEGF-D):

Its gene is located on chromosome xp22.31. VEGF-D acts on VEGFR-2 and VEGFR-3 **(Roy et al., 2006).**

It has a role in both angiogenesis & lymphanogenesis **(Baldwin et al., 2005).**

5- Vascular Endothelial Growth Factor-E(VEGF-E):

It is detected in the genome of the parapox virus which occasionally infects humans**.** VEGF-E acts on VEGFR-2 and NRP-1 causing endothelial cell mitogenesis and vascular permeability **(Roy et al .,2006)**.

6-Vascular Endothelial Growth Factor-F (VEGF-F):

VEGF-F including svVEGF from Bothrops insularis & Trimeresurns flavoviridis svVEGF (TfsvVEGF) from pit vipers in addition to Hypotensive Factor (HF), increasing capillary permeability protein (ICPP) and vamin from vipers. VEGF-F acts on VEGFR-1 and VEGFR-2 **(Takahashi and Shibuya, 2005).**

7-Placental Growth Factor(PLGF):

It was first identified in the placenta but now it is known to be present in hearts, lungs and skeletal muscles. Its gene is located on chromosome14q24 **(Roy et al.,2006).**

It has 4 isoforms: PLGF-1 (PLGF131), PLGF-2 (PLGF152), PLGF-3 (PLGF203) and PLGF-4 (PLGF224). **(Yang et al., 2003).**

PLGF-1 acts on VEGFR-1 while PLGF-2 acts also on NRP-1 and NRP-2 **(Yla-Herttuala and Alitala, 2003).**

Its action is either by direct effect on endothelial cells or by augmenting the action of VEGF **(Auterio et al., 2003).**

In addition it has a significant role in arteriogenesis (a promising treatment of ischemic diseases) **(Pippe et al., 2003).**

Functions of VEGF

1-Endothelial cell proliferation:

Endothelial cell proliferation appears to involve VEGFR-2 mediated activation of the mitogen-activated protein kinase as well as protein kinase C pathway **(Zachary and Gliki, 2001).**

2-Endothelial cell activation:

It appears that VEGF has different effects on the endothelial cell morphology, cytoskeleton alterations and stimulation of endothelial cell migration and growth **(Dvork, 2002).**

3-Endothelial cell survival:

It promotes cell survival by inhibiting apoptosis pathway, up-regulating antiapoptotic proteins such as Bl-2 and activating proteins like foal adhesion kinase (PI3K / AKT) which maintain endothelial cell survival despite apoptotic stimulai **(Dvork, 2002).**

4-Migration and invasion:

Degradation of the basement membrane is an essential step for cell migration, invasion and angiogenesis. VEGF induces a number of enzymes and proteins important for degradation of the basement membrane (including matrix-degrading metalloproteinases, metalloproteinase interstitial collagenase and serine proteases like urokinase-type plasminogen activator and tissue-type plasminogen activator) **(Zachary and Gliki, 2001).**

5-Vascular permeability:

VEGF appears to be one the most potent vascular permeabilizing agents. It has an effect which is 50,000 times greater than Histamine. It increases permeability in a variety of vascular beds (skin, wound, peritoneal wall, mesentery and diaphragm) and can lead to pathologic conditions like malignant ascites and malignant pleural effusion **(Dvork, 2002).**

VEGF-A can induce production of Nitric Oxide that increase vascular permeability. Also it acts as apro-