

**Comparative Study between the Effect of Low
Molecular Weight Heparin Alone and Low Molecular
Weight Heparin Combined with Sildenafil Citrate on
Intrauterine Growth Restriction**

Thesis

Submitted for Partial Fulfillment of Master Degree

in Obstetrics and Gynecology

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2018



Acknowledgement

First of all, all gratitude is due to **Allah** almight for blessing this work, untill it has reached its end, as a part of his generous help, throughout my life.

*Really I can hardly find the words to express my gratitude to **Prof. Dr. Ayman Abd-El Razek Abo-El Noor**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his generous supervision, continuous help and encouragement throughout this work. Also for tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

*I would like also express my sincere appreciation and gratitude to **Prof. Dr. Mohamed El-Mandooh Mohamed**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his continuous directions and support throughout the whole work.*

*I cannot forget the great help of **Dr. Heba Abd-El Basset Allam**, Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for her invaluable efforts, her guidance and for her patience and support to get this work into light.*

Also I would like to express my deep feelings and thanks to the staff of obstetric, and Neonatal Intensive Care Units in Ain Shams Maternity Hospital for their help.

*"
Last but not least, I dedicate this work to my family, without their sincere emotional support, pushing me forward, this work would not have ever been completed.*

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List of abbreviations

LMWH	low molecular weight heparin
IUGR	intrauterine growth restriction
FGR	fetal growth restriction
cGMP	cyclic Guanosine Mono Phosphate
PDE	phosphodiesterase
SGA	Small for gestational age
UA	umbilical artery
IVH	intraventricular haemorrhage
NEC	necrotizing enterocolitis
ACA	anticardiolipin antibodies
CMV	Cytomegalovirus
AGA	Appropriate for gestational age
BPD	Biparietal diameter
HC	head circumference
AC	abdominal circumference
FL	femur length
EFW	Estimated fetal weight
AFI	Amniotic fluid index
CRL	Crown_rump length
SFH	symphysio Fundal Height
LMP	last menstrual period
GA	gestational age
S/D ratio	systolic/diastolic ratio

RI	resistance index
PI	pulsatility index
MCA	middle cerebral artery
DV	Ductus venosus
DIGITAT	Disproportionate Intrauterine Growth Intervention Trial at Term
AEDF	Abscent End Diastolic Flow
REDF	Reversed End Diastolic Flow
GRIT	Growth Restriction Intervention Trial
NICU	neonatal intensive care unit
CST	contraction stress test
PSV	peak systolic velocity
EDV	end diastolic velocity
TAV	time averaged velocity
RCT	randomized controlled trial
RCOG	Royal College of Obstetricians and Gynecologists
ACOG	American College of Obstetricians and Gynecologists
NO	Nitric oxide
APS	Anti-phospholipid syndrome
DVT	deep vein thrombosis
PT	prothombin time
APTT	activated partial thromboplastin time
LSCS	Lower segment Caesarian section
PA	Placental abruption
TIPPS	Thrombophilia In Pregnancy Prophylaxis Study
PET	Pre-eclampsia toxaemia

T.i.d	three times a day
ICU	Intensive care unit
UtA	uterine artery
IUFD	intrauterine fetal demise

INTRODUCTION

Fetal Growth Restriction (FGR) is a problem where the fetus fails to attain its normal growth potential and this affects nearly about 8% of all pregnancies. (*Pilliod, et al., 2012; Wareing, et al., 2005; Villar, et al., 1982*)

The growth restricted fetuses are almost suffering a poor pregnancy outcome being at increased risk of perinatal complications mainly, fetal distress, asphyxia, neonatal hypoglycemia as well as poor feeding (*Villar, et al., 1982*). Second; they are more prone to long-term neurological and developmental disorders, increased incidence of hypertension, diabetes mellitus and coronary heart disease in adulthood. (*Villar, et al., 1982; Rodeck and Whittle, 1999*).

Abnormal formation and function of the placenta with subsequent placental insufficiency is considered as the main pathogenic mechanism involved in FGR. These pregnancies are commonly associated with elevated peripheral vascular resistance in the maternal arterial system as seen in pregnancies complicated with preeclampsia. (*Schiessl, et al., 2006*).

The trophoblastic production of nitric oxide in normal pregnancy plays an important role in vasodilatation at the fetoplacental circulation, thus improving fetal oxygen and nutritional supply (*Rosselli, et al., 1998*). This effect, in fact, is attributed to its potent relaxing effect on arterial and venous smooth muscle and perhaps inhibiting platelets aggregation and adhesiveness. (*Nanetti, et al., 2008*).

This is because sildenafil citrate, a selective inhibitor of cyclic Guanosine Mono Phosphate (cGMP)-specific phosphodiesterase (PDE)-5 is found to enhance the relaxation and accumulation of neural-released nitric oxide and consequently increases uterine blood flow and also potentiates estrogen-induced vasodilation. (*Jerzak., et al., 2008*).

Placental infarction is rare in otherwise normal pregnancies. In a recent single-centre retrospective cohort of 180 singleton pregnancies with placental infarction, the majority of placentas were small and exhibited histologic abnormalities in both the utero-placental vascular bed and in the development of the placental villi. (*Franco, et al., 2011*). These observations suggest that normal placental development confers intrinsic anticoagulant properties, via both hemostasis regulation at the

surface of the villi and the attainment of a high utero-placental blood flow velocity within the placenta due to erosion of the distal segments of the spiral arterioles by the invasive extravillous trophoblast cells. (*Drewlo, et al., 2010*).

It is based on the observation that the extent of placental infarction correlates with the severity of preeclampsia and intrauterine growth restriction (IUGR), (*Buyse, et al., 1974*), and the assumption that heparin effectively prevents placental infarction. (*Gris, et al.,2004*).

On the basis of preliminary researches, some centers are now adopting the treatment with sildenafil in cases of FGR; however, there is significant uncertainty as regard the true health benefits. Moreover, the potential harm is not yet excluded. (*Jakobsen, 2013*)

Some other studies found improved pregnancy outcome with FGR with or without preeclampsia when low molecular weight heparin (LMWH) and low dose aspirin were used in comparison with the control groups. (*Mutlu, et al., 2015; Neykova, et al., 2016*)

To the best of our knowledge few studies compared the effect of sildenafil citrate and heparin in the management of FGR, hence the aim to conduct our study.

Intrauterine Growth Restriction

Definitions and terminology

Intrauterine growth restriction (IUGR) is defined as a pathologic decrease in the rate of fetal growth below 10th percentile for age. (*Peleg, et al., 1998*) (Figure 1) The most frequent etiology for late onset FGR is uteroplacental dysfunction which is due to inadequate supply of nutrients and oxygen to support normal aerobic growth of the fetus. (*Trapani, et al., 2016*)

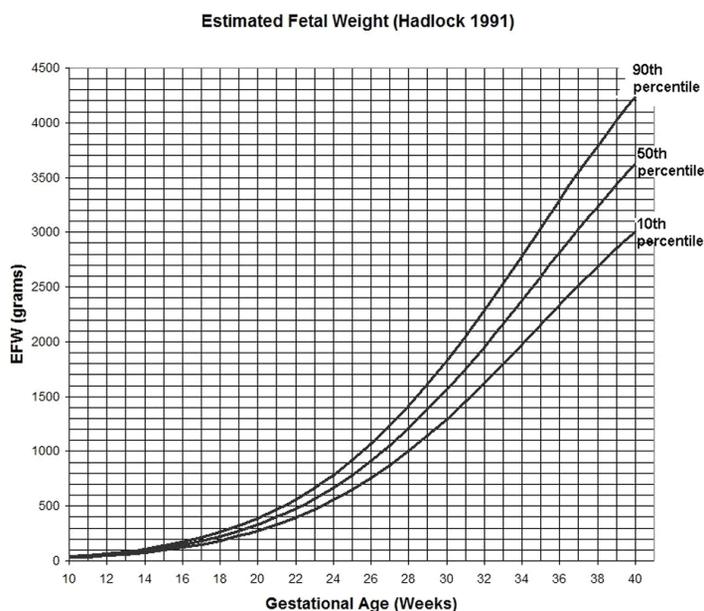


Fig. (1): %Estimated fetal weigh in grams according to gestational age in weeks growth chart (showing 10th, 50th and 90thpercentile) (*Hadlock, et al., 1991*)

Epidemiology/Incidence

By definition, 10% of fetuses will be diagnosed by FGR by population growth charts. Small for gestational age (SGA) complicates about 4% to 8% of pregnancies in developed countries and up to 25% of pregnancies in undeveloped countries.(*de Onis, et al., 1998*) Birth weight <3rd percentile carries the highest risk for perinatal morbidity [umbilical artery(UA) blood pH < 7.0, grade 3 or 4 intraventricular haemorrhage (IVH), respiratory distress, necrotizing enterocolitis (NEC) and sepsis] and mortality when compared against other cut-offs.(*McIntire, et al., 1999*)

Causes and etiological factors

The causes of FGR can be divided into three basic categories: maternal factors, fetal factors, and placental factors (Figure 2). While the pathophysiology of each factor is different, maternal factors (e.g., maternal medical disease) and placental factors may have a common final pathway of decreased placental perfusion and transfer of nutrients across the placenta to the fetus. Fetal factors describe scenarios where growth is reduced secondary to genetic, chromosomal, or infectious causes.(*Hendrix and Berghella, 2008*)