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

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LMWH	**low molecular weight heparin**
IUGR	**intrauterine growth restriction**
FGR	**fetal growth restriction**
cGMP	**cyclic Guanosine Mono Phosphate**
PDE	**phosphodieste-rase**
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 Cesarian 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 feto-placental 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 phosphodieste-rase (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)***

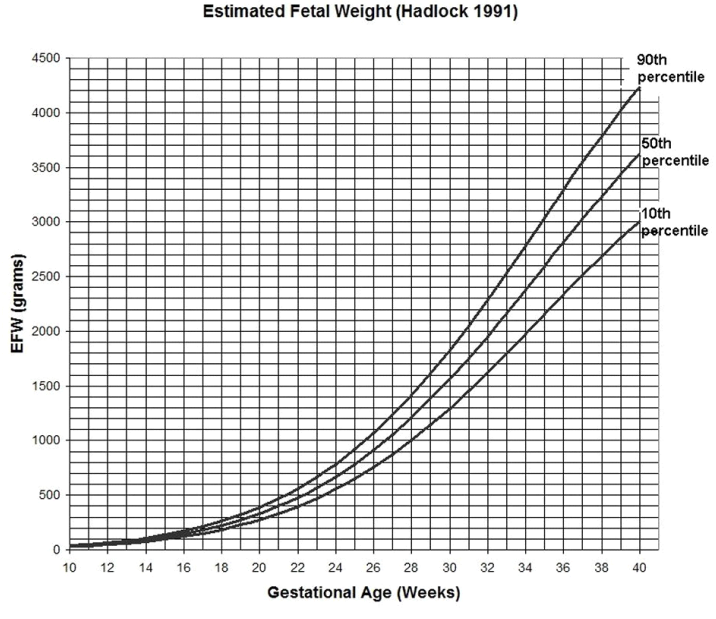

Fig. (1): **%**Estimated fetal weigh in grams according to gestational age in weeks growth chart (showing 10th, 50th and 90thpercentile) ***(Hadlock, et al., 1991)***

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)***