



Sildenafil versus Low Molecular Weight Heparin in fetal Growth Restriction Treatment: RCT

Thesis

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Dedication

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List of Abbreviations

Abb.	Full term
AC.....	Abdominal circumference.
AFI.....	Amniotic fluid index.
AFP.....	Alpha fetoprotein.
AGA	Appropriate-for-gestational age.
APA\$.....	Anti-phospholipid antibody syndrome.
APTT	Active partial thromboplastin time.
A/REDF.....	Absent/ reversed end-diastolic velocity.
B-HCG.....	Beta- human chorionic gonadotropin.
BMI.....	Body mass index.
BPP	Biophysical profile.
cGMP.....	Cyclic guanosine monophosphate.
CI	Confidence interval.
CMV	Cyto-megalo virus.
CPR.....	Cerebro-placental ratio.
CTG	Cardiotocography.
DCs.....	Dendritic cells.
DM.....	Diabetes mellitus.
DoHaD.....	Developmental origin of health and disease.
DVD	Ductus venosus Doppler.
E3.....	Estriol.
EDRF.....	Endothelium-derived relaxing factor.
EDV	End diastolic volume.
EFW.....	Estimated fetal weight.
EGF.....	Epidermal growth factor.

List of Abbreviations Cont...

Abb.	Full term
F/A	Femur to abdomen ratio.
FGR	Fetal growth restriction.
FHR	Fetal heart rate.
FL	Femur length.
FOAD	Fetal origin of adult disease.
GA	Gestational age.
HC.....	Head circumference.
HCG.....	Human chorionic gonadotrophin.
HMD.....	Hyaline membrane disease.
HTN.....	Hypertension.
IGFs	Insulin-like growth factors.
IgG	Immunoglobulins G.
IL-2.....	Interleukin-2.
IQ.....	Intelligence quotient.
IUFD.....	Intrauterine fetal demise.
IVF.....	In vitro fertilization.
LBW	Low birth weight.
LGA.....	Large-for-gestational age.
LMWH	Low molecular weight heparin.
MCA	Middle cerebral artery.
NADPH	Nicotinamide adenine dinucleotide phosphate-oxidase.
NICU	Neonatal intensive care unit.
NO	Nitric oxide.
NST.....	Non-stress test.
P5.....	5 th percentile.
PAPP-A	Pregnancy-associated plasma protein A.

, List of Abbreviations Cont...

Abb.	Full term
PDE-5	Phosphodiesterase type 5.
PET	Pre-eclampsia.
PI.....	Pulsatility index.
PlGF.....	Placental growth factor.
RCOG	Royal College of Obstetricians and Gynecologists.
RCT	Randomized control trial.
RDS	Respiratory distress syndrome
RI	Resistance index.
RPL.....	Repeated pregnancy loss.
S/D.....	The Systolic/ Diastolic ratio.
SB	Still birth.
SFH.....	Symphysis–fundal height.
SGA	Small-for-gestational age.
sGC	Soluble guanylate cyclase.
SLE	Systemic lupus erythematosus.
TCD	Transverse cerebellar diameter.
TGF- β	Transforming growth factor beta.
TNF- α	Tumor necrosis factor alfa.
TORCH.....	Toxoplasmosis, rubella, cytomegalovirus, herpes simplex.
UA RI	Umbilical artery resistance index.
UA	Umbilical artery.
UAD	Uterine artery Doppler.
UFH	Unfractionated heparin.
VTE	Venous thromboembolism.
VEGF.....	Vascular endothelial growth factor.
WHO.....	World Health Organization.

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Abstract

In conclusion, fetal growth restriction (FGR) remains one of the major challenges in the maternity care as well as one of the major causes of perinatal morbidity and mortality.

In the present study; we have presented data suggesting that, sildenafil and LMWH treatment may offer a new opportunity to improve perinatal outcomes for women whose pregnancies are complicated by FGR with improvement of the fetal growth parameters and reduction of NICU admissions. However, sildenafil carries more side effects despite tolerated.

The implications of sildenafil for increasing the fetal weight in FGR pregnancies showed significantly lower results than LMWH and have to be considered for future studies.

Keywords: Symphysis–fundal height - Soluble guanylate cyclase - Phosphodiesterase type 5

INTRODUCTION

Fetal growth restriction (FGR) refers to a condition in which a fetus is unable to achieve its genetically determined potential size. This definition intentionally excludes fetuses that are small for gestational age (SGA) but are not pathologically small. SGA is defined as growth at the 10th or less percentile for weight of all fetuses at that gestational age. Not all fetuses that are SGA are pathologically growth restricted and, in fact, may be constitutionally small (*Robinson, 2017*).

Almost 40% of all fetuses at or below the 10th percentile for growth are at high risk of potentially preventable perinatal death. Another 40% of these fetuses are constitutionally small. Because this diagnosis may be made with certainty only in neonates, a significant number of fetuses that are healthy, but SGA will be subjected to high-risk protocols and potentially, iatrogenic prematurity (*Yoshida et al., 2014*).

The remaining 20% of fetuses that are SGA are intrinsically small secondary to a chromosomal or environmental etiology. Examples include fetuses with trisomy 18, CMV infection, or fetal alcohol syndrome. These fetuses are less likely to benefit from prenatal intervention, and their prognosis is most closely related to the underlying etiology (*Robinson, 2017*).

FGR is actually more commonly due to extrinsic (utero-placental) insufficiency where gaseous exchange and nutrient delivery to the fetus become insufficient to allow it to thrive in utero (**Robinson, 2017**).

This process can occur primarily because of maternal diseases or conditions causing decreased oxygen-carrying capacity (e.g. cyanotic heart disease, hemoglobinopathies, smoking, substance abuse), or due to a dysfunctional oxygen delivery system secondary to maternal vascular disease (e.g. Hypertension whether chronic or pregnancy associated, diabetes mellitus (DM) with vascular disease, autoimmune disease causing vasculopathy, thrombophilia, chronic placental abruption, cord & placental anomalies) or due to twin-to-twin transfusion syndrome (**Robinson, 2017**).

Growth-restricted fetuses with severe impairment of umbilical artery (UA) blood flow are at increased risk of adverse outcomes such as intrauterine fetal demise and neonatal death, as well as increased neonatal morbidity, including hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis and respiratory distress syndrome (RDS) (**Korkalainen et al., 2017**).

Furthermore, epidemiological studies have shown that fetuses with FGR are predisposed to the development of cognitive delay in childhood as well as metabolic syndrome in adulthood (e.g. Obesity, DM, coronary artery disease and stroke) (**Sibley, 2017**).

To date, there is no known effective treatment for FGR. So, the current therapeutic goal is to deliver the most mature fetus while minimizing the risk to mother and reduce neonatal morbidity and mortality (***Figueras and Gratacós, 2014***).

In normal pregnancy, the trophoblast produces nitric oxide (NO), which is a potent venous and arterial vasodilator that also inhibits platelet aggregation. In pregnancies complicated by FGR, placental hypoxia and endothelial dysfunction are associated with decreased release of NO and increased phosphodiesterase type 5 (PDE-5) activity. Therefore, Isosorbide mononitrate (NO donor) and sildenafil citrate (PDE-5 inhibitor) have the potential for prevention as well as treatment of FGR (***Boeldt and Bird, 2017***).

Sildenafil citrate, a phosphodiesterase inhibitor (PDE5-selective inhibitor) enhances the effects of nitric oxide (NO), it acts by blocking the enzymes that break down cGMP, which mediates the effects of NO in the body and leads to vascular relaxation. As a vasodilator, sildenafil citrate can reduce vasoconstriction of myometrial small arteries, which may improve oxygen and nutritional supply to the fetus (***Huang and Lie, 2013***).

Heparin improve placental blood flow by inhibiting complement activation on trophoblast in addition to its anticoagulant effect through its action on antithrombin III and factor IIa (***Gris et al., 2010***).