THE EFFECT OF TRANSDERMAL PROPANETRIOL TRINITRATE ON: NITRIC OXIDE LEVEL, PLASMA THROMBOMODULIN LEVEL, UMBILICAL AND UTERINE DOPPLER FLOW VELOCIMETRY AND HYPERTENSION IN THE MANAGEMENT OF E.P.H.GESTOSIS

THESIS

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بسم الله الرحمن الرحيم

﴿ قَالُوا سُبْحَانَكَ لا عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا
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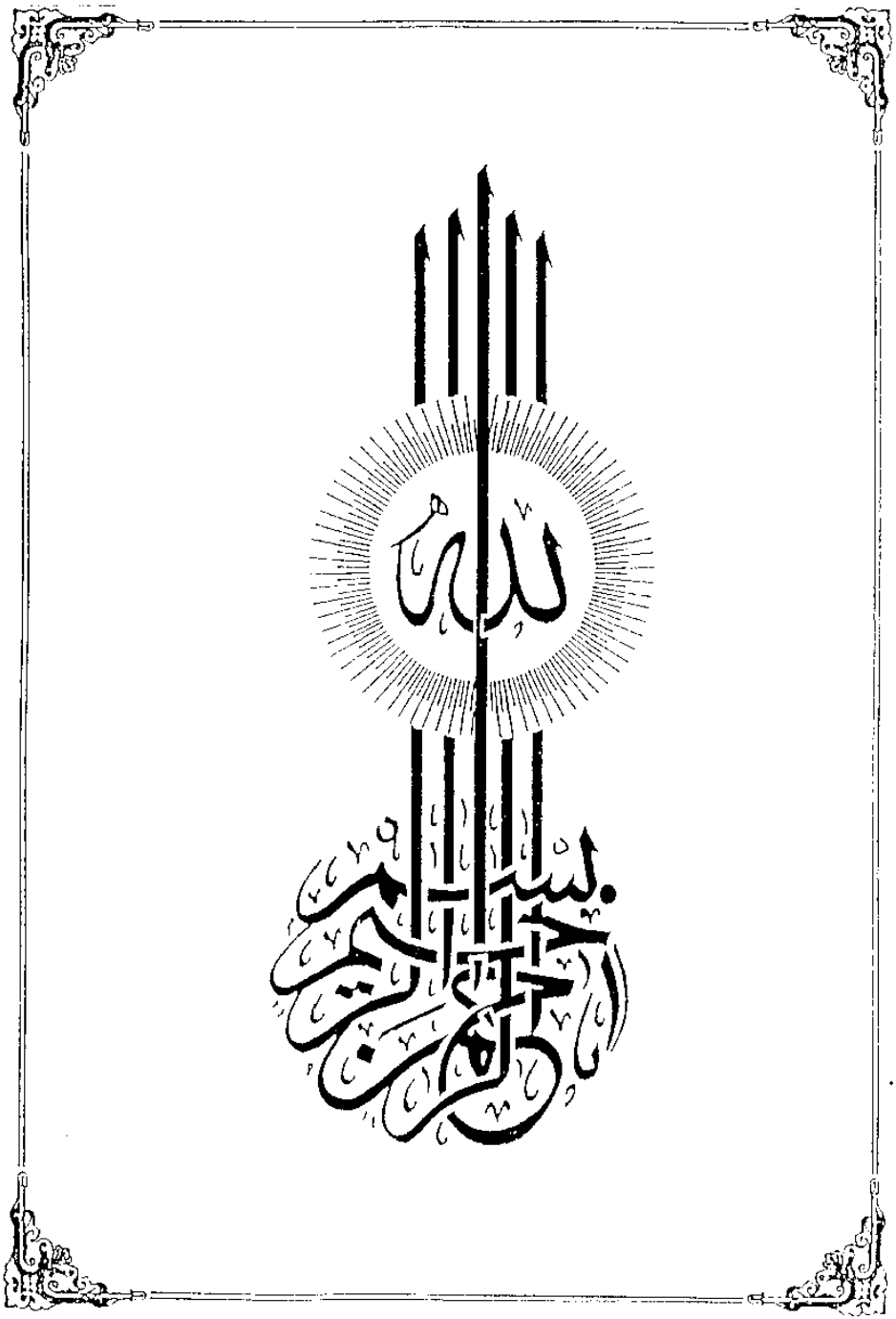

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ABSTRACT

Objective: To study the effect of nitric oxide donor (propanetriol trinitrate) on E.P.H. gestosis, the associated endothelial cell injury and fetal wellbeing.

Study design: The study comprised 50 pregnant patients between 28 and 38 weeks gestation with the diagnosis of mild or severe E.P.H. gestosis. For every patient a nitroglycerine patch (10mg) releasing transdermal propanetriol trinitrate was attached to skin of the abdomen and replaced daily for the desired duration of treatment.

A venous blood sample was taken from every patient before & immediately after the end of treatment for estimation of plasma nitric oxide levels by ELISA technique (Kits from R&D) systems Inc., Minneapolis MN USA) & plasma thrombodulin levels using Immubind thrombomodulin ELISA kit (American Diagnostica Inc. greenwhich, USA). Doppler ultrasound studies on the umbilical artery (measuring resistance index (RI) were carried out twice-weekly in addition to twice daily evaluation of blood pressure & presence of albuminuria. pregnancy was terminated in cases of severe uncontrolled hypertension after 48 hours of initiation of treatment, fetal distress, impending eclampsia or reaching maturity.

Results: The mean duration of treatment was about 5 weeks with the use of the patches, there was a significant decrease in both plasma thrombomodulin levels & RI by the end of treatment ($P<0.001$) in addition to a significant increase in plasma nitric oxide levels ($P<0.001$).

Conclusion: The use of nitric oxide donors provides a good chance for prolongation or pregnancy and improvement of pregnancy outcome in patients with E.P.H. gestosis in terms of decreasing the associated endothelial cell injury & improvement of fetal blood supply.

INDEX

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

A.C.O.G	American College of Obstetrician and Gynecologists
ADMA	Assymmetric dimethyl L-arginine
ADP	Adenosine diphosphate
APC	Activated protein C
ARDS	Adult respiratory distress syndrome
ATP	Adenosine triphosphate
C.N.S.	Central nervous system
c-AMP	Cyclic-adenosine monophosphate
c-DNA	Cyclic-deoxy ribonucleic acid
c-NOS	Constitutive nitric oxide synthetase
CW	Continuous wave
D.I.C	Disseminated intravascular coagulopathy
DM	Diabetus mellitus
E.P.H.	Edema, proteinuria and hypertension
EDRF	Endothelial derived relaxation factor
EGF	Epidermal growth factor
F.S.H.	Follicular stimulating hormones
FHR	Fetal heart rate
FVW	Flow velocity wave form
GnRH	Gonadotrophin releasing hormones
GTN	Glyceryl trinitrate
HELLP	Hemolysis, elevated liver enzymes and low platelet count
HPV	Hypoxic pulmonary vasoconstriction
HRP	Horse radish peroxidase
IL	Interleukin
i-NOS	Inducible nitric oxide synthetse
ISMN	Isosorbid mononitrate

ISSHP	International society for study of hypertension in pregnancy
IUGR	Intrauterine growth retardation
IUK:Cr	Inactive urinary kallikrein to creatinine ratio
L.H.	Luteinizing hormone
LDL	Low density lipoprotein
L-NAME	N^G nitro-L-arginic methyl ester
L-NMME	N^8 monomethyl-L-arginine
MAP	Mean arterial pressure
m-RNA	Messenger ribonucleic acid
NAC	N-acetyl cysteine
NANC	Non-adrenergic non-cholingergic neurones
NO	Nitric oxide
NOS	Nitric oxide synthetase
P.I.	Pulsatility index
P.I.H	Pregnancy induced hypertension
PAI-3	Plasminogen activator inhibitor-3
PCR	Polymerase chain reaction
PG	Prostaglandin
PW	Pulsed wave
R.I.	Resistant index
RPMC	Rat peritoneal mast cells
S.L.E	Systemic lupus erythematosis
S.N.P.	Sodium nitroprusside
S/D	Systolic diastolic ratio
TM	Thrombomodulin
TMB	Tetra-methyl benzidine
TNF	Tumour necrosis factor
TXA2	Thromboxane A2

INTRODUCTION

1

INTRODUCTION

Preeclampsia is a multisystemic pregnancy specific disorder, defined clinically as a syndrome of gestational hypertension, excessive proteinuria and/or generalised oedema *[Taylor et al., 1996]*.

Hypertension is the most common medical disorder associated with pregnancy and preeclampsia constitutes two thirds of cases of hypertension with pregnancy *[Seligman et al., 1994]*. Hypertensive disorders complicating pregnancy are common and along with haemorrhage and infection, they form a deadly triade that is responsible for a large number of maternal deaths *[Cunningham et al.,1993]*.

Investigation into the pathophysiology of pregnancy induced hypertension revealed that it is a syndrome of increased peripheral vascular resistance, coagulation abnormality, alteration in prostaglandin, nitric oxide (NO), lipid metabolism and tumour necrosis factor. It is considered to be a complex endothelial cell dysfunction which results in disturbance of the delicate balance between vasodilators such as prostacyclin and nitric oxide on one hand and vasoconstrictors such as angiotensin II, thromboxane A2 and endothelin on the other hand. Similarly, the balance between platelet activating and inhibiting factors has to be considered in the over-all function and picture of the disease *[Morris et al., 1996]*.

Endothelium-derived nitric oxide is proposed to play an important role in the lowering of the peripheral vascular resistance in normal pregnancy. In women with preeclampsia, the function of the endothelium is compromised and it is suggested that reduction of nitric oxide synthesis may contribute to the elevation of the blood pressure and activation of the coagulation pathway. also increased levels of factor VIII-related antigen and fibronectin play a role in the pathogenesis *[Ballegeer et al.,1990]*.

An elevated level of nitric oxide throughout pregnancy in normotensive pregnant women contributes to maternal vasodilatation, immunosuppression and maintenance of uterine relaxation. Among the hypertensive disorders, the difference in the clinical features between patients with essential hypertension may be due to plasma concentration of NO *[Nobunaga et al.,1996]*.

Local production of the endogenous vasodilator nitric oxide is important for fetoplacental circulation and reduced production of this substance has been demonstrated in endothelial cells from the umbilical cord in pregnancy-induced hypertension *[Pinto et al.,1991]*. Circulating level of nitrate (metabolite of nitric oxide) have been found to be decreased in patients with preeclampsia *[Seligman et al., 1994]*.

Thrombomodulin is one of the important biomarkers of endothelial cell damage and can be used for assessment of severity, progression or regression of pregnancy induced hypertension *[Shaarawy et al., 1996]*.