# STUDY OF SERUM LEVEL OF SOLUBLE ENDOGLIN IN PREGNANT WOMEN WITH PRE-ECLAMPSIA

**Thesis**
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## SOLUBLE ENDOGLIN:

# LIST OF ABBREVIATIONS

| | | |
|---|---|---|
| **ACE** | : | Angiotensin converting enzyme |
| **ACOG** | : | American colleage of Obstetrics and Gynecology |
| **ALT** | : | Alanine aminotransferase |
| **AM** | : | Adrenomedullin |
| **ANGII** | : | Angiotensin II |
| **AST** | : | Aspartate aminotransferase |
| **AT1** | : | Angiotensin II receptor-1 |
| **AT1-AA** | : | Angiotensin II receptor-1 autoantibodies |
| **Ca++** | : | Calcium ions |
| **CBC** | : | Complete blood count |
| **CO** | : | Carbon monoxide |
| **CTB** | : | Cytotrophoblast |
| **DBP** | : | Diastolic blood pressure |
| **DNA** | : | Deoxyribo-nucleic acid |
| **ECM** | : | Extracellular matrix |
| **ELISA** | : | Enzyme-linked immunosorbent assay |
| **eNOS** | : | Endothelial nitric oxide synthase |
| **Flt-1** | : | fms-like tyrosine kinase-1 |
| **GA** | : | Gestational age |
| **HELLP** | : | Hemolysis, elevated liver enzymes and low platelets |
| **HIF-1α** | : | Hypoxia-inducible transcription factor-1 alpha |
| **HO-1** | : | Heme oxygenase-1 |
| **IFN** | : | Interferone |
| **IL** | : | Interleukin |
| **IUGR** | : | Intrauterine growth restriction |
| **KDa** | : | Kilo Dalton |
| **LDH** | : | Lactate dehydrogenase |
| **mAB** | : | Monoclonal antibody |

| | | |
|---|---|---|
| **MDL** | : | Minimum detectable limit |
| **MMPs** | : | Matrix metallproteinases |
| **mRNA** | : | Messenger RNA |
| **MTHFR** | : | Methylenetetrahydrofolate reductase |
| **NADP** | : | Nicotinamide-adenine dinucleotide phosphate |
| **NO** | : | Nitric oxide |
| **NOS** | : | Nitric oxide synthase |
| **PAIs** | : | Plasminogen activator inhibitors |
| **PCR** | : | Polymerase chain reaction |
| **PlGF** | : | Placental growth factor |
| **RAS** | : | Renin-angiotensin system |
| **RNA** | : | Ribonucleic acid |
| **ROC** | : | Receiver operating characteristic |
| **ROS** | : | Reactive oxygen species |
| **RT-PCR** | : | Reverse transcriptase PCR |
| **SBP** | : | Systolic blood pressure |
| **sFlt-1** | : | Soluble fms-like tyrosine kinase-1 |
| **TGF-β1** | : | Transforming growth factor beta-1 |
| **TNF-α** | : | Tumor necrosis factor-alpha |
| **VEGF** | : | Vascular endothelial growth factor |
| **VEGFR-1** | : | Vascular endothelial growth factor receptor -1 |



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# INTRODUCTION

Pre-eclampsia is a multi-system pregnancy-specific hypertensive syndrome that causes substantial maternal and fetal morbidity and mortality. The lack of an effective test for identification of women at risk of developing pre-eclampsia remains a contributing factor for the high morbidity of the disease. In most developing countries, where the incidence of the disease is high, women present late with complications **(Levine et al., 2007).**

Although pre-eclampsia is called the disease of theories, the overwhelming evidence points to endothelial dysfunction as the central mechanism in the pathogenesis of the maternal syndrome in pre-eclampsia. The causes of this endothelial dysfunction remain elusive. However, poor placentation has been proposed as a major factor **(Sharon et al., 2008).**

Ischemic placenta secretes soluble factors into the maternal vasculature which have been implicated in inducing the endothelial dysfunction and the clinical features of pre-eclampsia. Excess secretion of a naturally occurring anti-angiogenic molecule of placental origin referred to as soluble endoglin (sEng) may contribute to the pathogenesis of pre-eclampsia **(Levine et al., 2006).**

Soluble endoglin acts by antagonizing an angiogenic and vasodilator molecule known as transforming growth factor beta-1 (TGF-β1) which is important not only in angiogenesis but also in keeping the lining of the blood vessels healthy. As a result, the cells

lining the blood vessels begin to sicken and die, the blood pressure increases and the blood vessels leak protein into the tissues and urine **(Levine et al ., 2006).**

Soluble endoglin is elevated not only during clinical pre-eclampsia but also 2-3 months before onset of clinical symptoms. It was also suggested that sEng correlates with disease severity and falls after delivery. Therefore, this anti-angiogenic protein in the maternal blood is a subject of research as a potential diagnostic and screening test for pre-eclampsia **(Stepan et al., 2007).**

## AIM OF THE WORK

The aim of the present study is to evaluate the clinical utility of serum soluble endoglin in diagnosis of pre-eclampsia and assessment of severity of the disease.

# PRE-ECLAMPSIA

## I) Definition:

Pre-eclampsia is a multi-system disorder of unknown cause that is unique to human pregnancy. Although definitions differ, many define pre-eclampsia as sudden onset of acute hypertension, with blood pressure ≥ 140/90 mmHg, presenting after the 20th week of gestation accompanied by abnormal edema and/or proteinuria, or both. It is considered severe if blood pressure and proteinuria are increased substantially or symptoms of end-organ damage, including fetal growth restriction, occur **(Sharon et al., 2008).**

Pre-eclampsia may also occur in the immediate post-partum period or up to 6-8 weeks post-partum. This is referred to as "post-partum pre-eclampsia". The most dangerous time for the mother is the 24-48 hours post-partum and careful attention should be paid to pre-eclampsia signs and symptoms **(Reynolds et al., 2006).**

## II) Epidemiology:

Pre-eclampsia affects 5%–7% of all pregnancies worldwide and approximately 3% of pregnant women in the western world. It is a major cause of preterm birth, intrauterine growth restriction and maternal mortality accounting for 12-18 % of pregnancy-related maternal deaths especially in developing countries.

In the United States, pre-eclampsia occurs in 6-8% of all pregnancies. Over 100,000 women are treated for pre-eclampsia per

year and approximately 21,000 women develop severe pre-eclampsia. Approximately 18% of maternal deaths in the United States are attributed to hypertensive disorders and pre-eclampsia, and several hundred women die from eclampsia and its complications every year. In the Netherlands its incidence in pregnancy is varying between 2% and 7% **(Roberts et al., 2005).**

In developing countries, pre-eclampsia affects 4.4% of all deliveries and may be as high as 18% in some countries in Africa. 50,000 cases of women experiencing life threatening eclamptic convulsions can be expected each year. In Egypt, about 40,946 of 76,117,421 estimated pregnant females suffer from pre-eclampsia yearly **(Aida et al., 2006).**

## III) Risk Factors for Pre-eclampsia:

There are many risk factors for pre-eclampsia including pregnancy-associated factors, maternal-specific factors and paternal-specific factors (Table 1) **(Dekker and Sibai, 2001).**

**Table (1):** Risk factors of pre-eclampsia:

| |
|---|
| • **Pregnancy-associated factors:** |
| - Hydatidiform mole.<br>- Hydrops fetalis.<br>- Multi-fetal pregnancy.<br>- Oocyte donation or donor insemination. |
| • **Maternal-specific factors:** |
| - Chromosomal abnormalities.<br>- Age greater than 40 years.<br>- Age less than 20 years.<br>- Black race.<br>- Family history of pre-eclampsia.<br>- Nulliparity.<br>- Pre-eclampsia in a previous pregnancy.<br>- Specific medical conditions: gestational diabetes, type I diabetes, obesity, chronic hypertension, renal disease and thrombophilias.<br>- Nutritional factors as decreased calcium and vitamin C in diet. |
| • **Paternal-specific factors:** |
| - First-time father.<br>- Previously fathered a pre-eclamptic pregnancy in another woman. |

**(Dekker and Sibai, 2001)**

**A. Pregnancy-Associated Factors:**

Evidence points to the placenta as a key source of factors that lead to the maternal endothelial cell dysfunction in pre-eclampsia. This is evident in that the clinical signs and lesions of pre-eclampsia remit within days after termination of pregnancy. The disease can occur in non-embryonic pregnancy (hydatidiform mole), suggesting that the presence of a fetus is not strictly necessary **(Page, 2000).** Also, pre-eclampsia is more common in the presence of a greater trophoblastic mass for instance in multiple pregnancy. The frequency

and severity of the disease are substantially higher in women with multifetal gestation as reported by **Wen and his colleagues (2004).** The maternal immune system also increases the risk of pre-eclampsia. This includes women who are pregnant by donated gametes i.e., donor insemination, oocyte donation, or even embryo donation. The use of donated gametes will affect the maternal-fetal immune interaction, and many of these women will have multi-fetal gestations **(Einarsson et al., 2003).**

**B- Maternal-Specific Factors:**

**1- Chromosomal abnormalities:**

Genome-wide linkage studies have identified at least three pre-eclampsia loci showing substantial linkage: 2p12, 2p25,46 and 9p13.46. These loci segregate with different populations **(Caulfield et al., 2003). Oudejans and colleagues (2004)** confirmed the susceptibility locus on chromosome 10q22.1 to be involved in pre-eclampsia.

**2- Age:**

Pre-eclampsia occurs more frequently at the extremes of the reproductive period. These include women who are younger than 20 years and those who are older than 40 years **(Wen et al., 2004).**

**3- Race:**

Some studies indicate that pre-eclampsia-related fatalities occur three times more often in black women than in white women. Although the precise reasons for the racial differences remain elusive, the differences may be indicative of disparities in health