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Serum tumor necrosis factor-α level and uterine artery Doppler indices at 11–13 weeks' gestation for preeclampsia screening in low-risk pregnancies: a prospective observational study

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ABSTRACT

Preeclampsia affects 1–2% of human pregnancies with no effective screening test. Studies have found some association between cytokines/other biomarkers and the later onset of preeclampsia. The challenge has been to find indicators with sufficient positive predictive value. A prospective observational study recruiting 500 low-risk pregnant women was carried out. Serum TNF-α and uterine artery Doppler were measured at 11–13 weeks. TNF-α cut-off value ≥14 pg/mL had a sensitivity of 67.8% and a specificity of 98% in predicting PE with PPV of 79.4% and NPV of 96.4%. Mean uterine artery PI ≥1.7 had a 100% sensitivity and 84.4% specificity in predicting PE, with a PPV of 41.7% and NPV of 100%. When combining both parameters together we had 88.6% sensitivity and 100% specificity in predicting PE with a PPV of 100% and NPV of 98.6%. Serum TNF-α assay improves the performance of mean uterine artery PI at 11–13 weeks for PE screening and the combination of both tests can rule out PE in the case of normal results.

1. Introduction

Preeclampsia is a unique human pregnancy disorder associated with significant maternal, perinatal mortality, and morbidity. It affects about 6–8% of pregnancies and accounts for 15% of maternal mortality in the United States (National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy, 2000).

Preeclampsia is believed to be caused by impaired trophoblastic tissue invasion of the maternal spiral arteries leading to placental ischemia and release of proinflammatory cytokines that cause generalized endothelial damage, contributing to many of the pathophysiological changes associated with preeclampsia (Granger et al., 2001; Johnson et al., 2002).

Several studies have reported that the maternal serum concentration of the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and its soluble receptor-1 (TNF-R1) is significantly higher in patients with preeclampsia than in normotensive individuals (Schipper et al., 2005).

In preeclampsia, defective trophoblastic invasion of the spiral arteries leads to a failure of conversion of high-resistance blood vessels to low-resistance blood vessels, resulting in impaired placental perfusion – a phenomenon that can be detected by Doppler studies of the uterine

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arteries (Plasencia et al., 2007). Nelson et al. (2014) suggested the presence of two preeclampsia phenotypes depending on the gestational age at the time of presentation. Characteristic findings of preeclamptic patients presenting at <34 weeks' gestation include small for gestational age fetuses, placental ischemia, and reduced placental size, while those in patients presenting at >34 weeks' gestation include appropriate for gestational age fetuses and large placental size. According to the uterine reinnervation theory, the findings in both cases appear to result from uterine nerve injury at different anatomical sites. However, cytokine release following uterine vasomotor nerve injury results in placental ischemia, while myometrial tension on injured nerves in the extraplacental myometrium results in the second phenotype, a mechanism supporting the mechanical distension theory (Nelson et al., 2014; Quinn, 2014).

During the past two decades, investigators have attempted to accurately predict the development of preeclampsia with the aid of various biochemical markers and uterine artery Doppler indices. However, only a persistent uterine artery Doppler diastolic notch beyond 22–26 weeks' gestation has proved to be associated with defective trophoblastic tissue invasion and shown to be the main predictive factor for preeclampsia (Edkker, 2003).

This study was aimed at investigating the validity of the combined measurement of serum TNF-α levels and uterine artery Doppler indices at 11–13 weeks' gestation in the early screening for preeclampsia in a low-risk population.

2. Patients and methods

2.1. Study design and settings

This was a prospective study carried out at Ain Shams University Maternity Hospital between January 2013 and August 2013.

2.2. Study population

Consecutive low-risk preeclampsia participants attending the Ain Shams University Maternity Hospital Antenatal Care Clinic were recruited. Inclusion criteria were singleton pregnancies between 11 and 13 weeks' gestation, primigravidity, spontaneous conception, and no history of infertility, hypertension, diabetes, or immunological, endocrine, and/or chronic renal diseases. Multiparous women, women with multiple pregnancies, those with a history of hypertension, endocrine, immunological, and chronic renal diseases, smokers, and women with a body mass index (BMI) $\geq 26\,kg/m^2$ were excluded from the study.

2.3. Intervention

The participants underwent a complete medical history assessment, thorough general and pelvic examination, obstetric ultrasound, and basic laboratory investigations (complete blood count, blood group, Rhesus factor [Rh], urinalysis, and a random blood sugar test) at the first visit. Participants were then followed up every month until the end of the second trimester, every 2 weeks until the end of the 36th week, and every week until delivery. Arterial blood pressure (BP) was measured at every visit and urinalysis was performed. All participants underwent routine obstetric ultrasound and were screened for gestational diabetes. Blood samples were collected between 11 and 13 weeks' gestation for TNF-α level measurement after obtaining consent.

Preeclampsia was diagnosed according to the National High Blood Pressure Education Program Working Group using the high BP in pregnancy criteria. Hypertension was defined as repeated systolic BP ≥140 mmHg (Korotkoff phase 1) and diastolic BP ≥90 mmHg (Korotkoff phase 5), respectively.

Proteinuria was defined as the presence of >300 mg of protein in a 24-h urine collection sample, or repeated >1+ proteinuria on dipstick analysis (National High Blood Pressure Education Programme Working Group on High Blood Pressure in Pregnancy, 2000).

Participant data were obtained from their medical records after delivery.

2.4. Uterine artery Doppler

Transabdominal uterine artery Doppler was carried out at 11–13 weeks' gestation using a MedisonSonoAceX6 ultrasound system (Samsung Medison Co., Ltd.) with a convex multiple frequency (3–7 MHz) probe by the same operator. The transducer was gently tilted from side to side and color-flow mapping was used to identify each uterine artery along the side of the cervix and uterus, at the level of the internal os.

Pulsed-wave Doppler was used with the sampling gate set at 2 mm to cover the whole vessel and care was taken to ensure that the angle of insinuation was <30° when three similar consecutive waveforms had been obtained. The uterine artery pulsatility index (PI) from the left and right arteries was measured, and the mean PI was calculated.

2.5. Laboratory methods

Blood samples were collected between 11 and 13 weeks' gestation into a serum separator tube. After clot formation, samples were centrifuged at $2000 \times g$ for 10 min and the serum separated. Undiluted serum samples were stored at −20 °C or below for up to 3 months for later use. Serum samples were diluted 1:2 in a mixture with a diluent and tested using enzyme-linked immunosorbent assay with a murine monoclonal antibody specifically for human TNF-α. The minimum detectable TNF-α concentration was >10 pg/mL.

2.6. Statistical methodology

The sample size was calculated using an online statistical program. Using serum TNF-α concentrations and calculating the standard deviation (SD) from their total population and the standard error of the mean (SEM) as described by (Michael et al., 2008), it was determined that 17 individuals were needed to detect a difference between