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The Prediction of Adverse Pregnancy Outcome Using Low Unconjugated Estriol in the Second Trimester of Pregnancy without Risk of Down's Syndrome

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Abstract

To investigate the relationship between low unconjugated estriol (uE3) levels in the second trimester and adverse perinatal outcomes in pregnancies without increased risk for Down's syndrome, 1,096 women under 35 years of age underwent a mid-trimester AFP-hCG-uE3 screening test between January 1995 and June 1998. Multiple pregnancies, maternal diabetes, smoking and elevation of AFP and hCG levels more than 2.0 multiple of median (MoM) were excluded from our study population. The results were divided into a low-uE3 group with uE3 levels at or below 0.75 MoM and a normal uE3 group with uE3 levels above 0.75 MoM. The risk for adverse pregnancy outcome was compared between the two groups and the role of low uE3 as a predictor of adverse pregnancy outcome was determined. The data were assessed using χ^2 or Fisher exact test and then logistic regression was used for the final analysis. The odds ratio (OR) and corresponding 95% confidence intervals (CI) were also calculated. Unconjugated E3 levels at or below 0.75 MoM was significantly associated with fetal growth restriction after adjustment for maternal age, weight, sampling weeks, AFP and hCG levels (OR 0.413, 95% CI 0.174−0.900; P=0.035). Low uE3 levels in the second-trimester could help in the detection of fetal growth restriction by a low risk group in Down's syndrome. Careful gestational dating and serial clinical and sonographic assessment of fetal growth may be required for the clinician to manage these parturients.

Key Words: Unconjugated estriol, fetal growth, pregnancy outcome, second-trimester, screening program

INTRODUCTION

Second-trimester maternal serum alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) and unconjugated estriol (uE3) have been used as screening markers for Down's syndrome. Recently, clinically important outcomes have been associated with the so-called unexplained abnormal plasma markers. Unexplained elevated AFP in the second trimester of pregnancies is associated with low birth weight, preterm delivery, pregnancy-induced hypertension, and placental abruption.[1] Patients with elevated hCG alone appear to be at higher risk of pregnancy-induced hypertension, low birth weight, preterm labor, and small size for gestational age.[2,3] Estriol was used as measurement of fetal welfare in the mid-1960s to mid-1970s. Serial 24-hour urine E3 measurements were obtained in the third trimester and the decline of E3 or its failure to rise was associated with pregnancy-induced hypertension, diabetes mellitus, postdates, fetal growth restriction, and fetal death.[4,5] However, the tests were inefficient, in collection and more expensive than nonstress test, and were subsequently abandoned as a generally-used fetal assessment tool.

Measurement of uE3 in maternal serum has been reintroduced as one of the screening markers for Down's syndrome in the second trimester. The synthesis of estriol is dependent on the fetal adrenal cortex, the fetal liver and placental. Estriol diffuses into the maternal compartment, where it can be measured as uE3, its rise in concentration paralleling the growth of fetus and placenta.[6] For that reason, it was thought to be a more sensitive indicator of altered fetal metabolism than any other maternal

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serum marker. Low uE3 values related to adverse pregnancy outcomes were reported, but much less was known than from AFP and hCG. In this study, we investigated the relationship between low uE3 levels in the second trimester and adverse perinatal outcomes in pregnancies without increased risk for Down's syndrome.

MATERIALS AND METHODS

A total of 1,096 women underwent the second-trimester AFP-hCG-uE3 screening program and delivered at Yonsei Medical Center between January 1995 and June 1998. All women in this study were under 35 years of age at the time of screening and had a singleton pregnancy between 15 and 21 weeks' gestation. Multiple pregnancies, maternal diabetes, smoking and elevation of AFP and hCG levels more than 2.0 multiple of median (MoM) were excluded from our study population to prevent confounding the predictive role of low uE3. They were then divided into two groups: uE3 levels at or below 0.75 MoM, and above 0.75 MoM. The threshold of 0.75 MoM was selected on the basis of an observation by Pergament et al.[7] of an association between uE3 of 0.75 MoM or below and an adverse pregnancy outcome. We also examined the distribution of maternal demographic variables which included maternal age, parity, maternal weight, sampling weeks, AFP and hCG between low and normal uE3 groups.Six adverse pregnancy outcomes were studied; preterm delivery (defined as those who delivered before 37 weeks gestation with or without premature rupture of membrane); fetal growth restriction(below the 10th percentile of expected fetal weight measured sonographically for given gestational age); fetal distress (Apgar score less than 7 at 5 minutes); preeclampsia (persistent blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic and proteinuria of at least 0.3 g/24 h); and fetal anomalies and fetal death. The risk for adverse pregnancy outcome was compared between the two groups and the roles of low uE3 as a predictor of adverse pregnancy outcome was determined.

The demographic variables were assessed using a T-test, and adverse pregnancy outcomes were evaluated using χ^2 or Fisher exact test for matched data. Logistic regression was used for the final analysis, which the odds ratio (OR) and corresponding 95% confidence interval (CI) were also calculated.

RESULTS

One hundred and seven women were below 0.75 MoM in the low uE3 group (9.76%) and 989 women were above 0.75 MoM in the normal uE3 group. Mean maternal age, the sampling weeks and maternal weight were no different between the two groups. However, the AFP levels were significantly lower in the low uE3 group than the normal uE group (p=0.001), while hCG levels were significantly higher in the low uE3 group than in the normal uE3 group (p=0.001) (Table 1). Adverse pregnancy outcomes had occurred in 26 of 107 women (24.3%) in the

Table 1. Demographic Variables between Low and Normal uE3 Groups

Variables	Low uE3 (n=107)	NL uE3 (n=989)
Maternal age (olds)	29.0±2.6	28.5±2.9
Sampling weeks	16.6±1.6	16.6±1.3
Maternal weight (kg)	53.8±6.1	55.2±7.5
AFP (MoM)	0.84±0.3	1.00±0.3*
hCG (MoM)	1.13±0.5	0.96±0.5†

AFP, alpha-fetoprotein; hCG, human chorionic gonadotropin; uE3, unconjugated estriol; MoM, multiple of median.
*p=0.001.
†p=0.001.

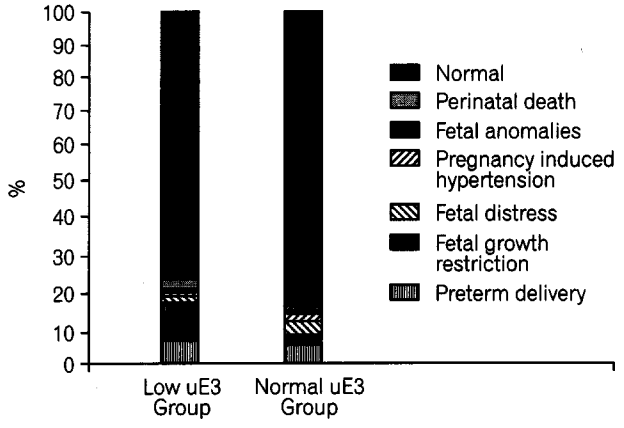

Fig. 1. Adverse pregnancy outcomes between low and normal uE3 groups.

Table 2. Comparison of Adverse Pregnancy Outcomes between Low and Normal uE3 Groups

Outcomes	Low uE3	NL uE3	Total
Preterm delivery	7	54	61
FGR	12*	28	40
Fetal distress	2	36	38
PIH	1	23	24
Fetal anomalies	1	8	9
Fetal death	3	13	16
Total	26†	162	188

uE3, unconjugated estriol; FGR, fetal growth restriction; PIH, pregnancy induced hypertension.
*p=0.003.
†p=0.018.

low-uE3 group and 162 of 989 (16.4%) in the normal uE3 group. There were significantly more adverse pregnancy outcomes in the low-uE3 group than in the normal uE3 group (p=0.018) (Fig. 1). In the low-uE3 group, the development of fetal growth restriction was significantly higher compared with the normal uE3 group (p=0.019). But preterm delivery, fetal distress, preeclampsia, fetal anomalies and fetal death were not significantly different between the low and normal uE3 groups (Table 2). After adjustments for maternal age, sampling weeks, maternal weight, AFP and hCG levels, women in the low uE3 group were found to have significantly higher odds for developing fetal growth restriction than women with normal levels of uE3 (OR 0.413; 95% CI 0.174−0.900; p=0.035).

DISCUSSION

The triple marker screening has a sensitivity in the prediction of Down's syndrome of more than 60%.[8] Together with hCG and AFP, the measurement of unconjugated E3 in maternal serum is a useful second trimester screening marker for Down's syndrome.[9] As well the association between unexplained second trimester decreased or low uE3 levels and adverse pregnancy outcomes have been reported.[7,10] Reduced or persistently low levels of maternal plasma uE3 have been observed in pregnancies, complicated by chronic hypertension, preeclampsia, intrauterine growth retardation and diabetes mellitus, and as a predictor of impending fetal demise.[11,12] Unexplained low uE3 levels may result not only from fetal abnormality, but also from placental pathology. The level of E3 in maternal plasma is also dependent on fetal and placental steroidogenic cooperation and the availability of the precursor, dehydroepiandrosterone, synthesized by the fetal adrenal gland. Reduction in uteroplacental blood flow is also associated with decreased production of unconjugated E3; therefore, lowered E3 levels in the second trimester could reflect fetal or placental dysfunction, predisposing toward an adverse pregnancy outcome.[13] Maternal serum uE3 levels increased in a log-linear fashion by about 20% per week from 15 to 20 weeks gestation and were about 15% lower in smokers than in nonsmokers. Two factors such as diurnal variation and smoking have been reported to influence maternal serum uE3 levels.[14] Controlling for these factors in a screening program limits the utility of maternal uE3 levels as a marker for adverse pregnancy outcome. Duration of storage and maternal weight had only a small effect on the concentration of serum uE3 while maternal age had no discernible effect.[9] If both AFP and hCG levels are greater than 2.0 MoM, the incidence of fetal compromise is increased.[15-17] In studies evaluating levels of uE3 in relation to pregnancy outcome, patients were selected according to certain cutoff points and our study evaluated the role of uE3 according to a certain cutoff point and assessed the relative contribution of uE3 to adverse pregnancy outcome. Pergament et al. suggested that uE3 levels at or below 0.75 MoM in the second trimester correlated better with an adverse pregnancy outcome than AFP and hCG levels in patients with increased risk of Down's syndrome.[7] Kowalczyk et al. also suggested using the same threshold, that low second trimester levels of uE3 are associated with fetal growth restriction, low amniotic fluid index, and small size for gestational age.[9] In our study, all women had normal levels of serum AFP and hCG (below 2 MoM), although patients with low uE3 levels tended to have higher hCG levels than patients with normal uE3 levels (0.99 versus 0.96 MoM). Undetectable low levels of uE3 have been associated with placental sulfatase deficiency and increased in association with male gender.[14] But we did not find such a case. Rather low E3 levels could be associated with either a placental or a fetal pathologic condition. Vascular flow studies of fetal vessels and histologic

evaluation of placental tissue might help to determine the relationship between low estriol levels and impaired perinatal growth. More extensive data collections and prospective maternal serum uE3 levels are needed to assess the magnitude of the association, its sensitivity and specificity, and the extent to which it is independent of maternal age, AFP and hCG. Another advantage of measuring maternal serum uE3 in second trimester to direct ultrasonographic scanning would lead to earlier detection of impaired fetal growth.[18] Such a protocol, making sequential use of biochemical markers and ultrasonography, should allow the detection of adverse pregnancy outcomes. In our study, low uE3 levels in the second trimester appeared to be associated with fetal growth restriction and this was independently associated with some risk factors in fetal growth. Further prospective studies are required to confirm low unconjugated estriol levels in relationship to impaired fetal growth.

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