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정상 산모와 태아 발육 지연이 있는 산모에서 모체 혈청과 제대혈 prealbumin의 임상적 의의

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Maternal Serum and Fetal Cord Blood Levels of Prealbumin in Normal and Intrauterine Growth-Restricted Pregnancies

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Objectives: (a) To assess the changes in maternal serum prealbumin levels during normal gestation, (b) to compare the paired maternal serum and fetal cord blood prealbumin levels of normal and intrauterine growth restricted pregnancies, and (c) to determine the relationship between the maternal serum and cord blood prealbumin levels and fetal birth weight.

Methods: Maternal serum prealbumin levels were measured in: (a) Normal pregnant women in the first (*n*=25), second (*n*=20) and third (*n*=25) trimester with appropriate for gestational age (AGA) fetuses; and (b) pregnant women with intrauterine growth restriction (IUGR) at delivery (*n*=15). Corresponding fetal cord blood prealbumin levels from the AGA group in the third trimester (*n*=25) and the IUGR group (*n*=15) were obtained during delivery. The prealbumin concentrations were quantified by immunoturbidmetric assay.

Results: There was no significant correlation between the gestational weeks and maternal serum prealbumin levels during normal gestation. However, the maternal serum prealbumin concentrations from the third trimester were significantly lower than those of 1st and 2nd trimester. Furthermore, there was no significant difference between the maternal serum and cord blood prealbumin level of the control and those of IUGR group of third trimester. Moreover, there was no significant relationship between fetal and maternal level of prealbumin and fetal birthweight for both normal and IUGR pregnancies.

Conclusion: Maternal serum and fetal cord blood prealbumin level was not an independent predictor of birth weight or fetal growth restriction. The failure to demonstrate a positive relationship may be due to the complex physiologic changes associated with pregnancy.

Key words: Prealbumin, Intrauterine growth restriction, Nutritional parameter, Fetal cord blood

Maternal metabolism undergoes a series of metabolic adaptations and plays a critical role during pregnancy to sustain the growth of fetus and placenta.[1] Available evidence suggests that fetal growth is most vulnerable to maternal dietary deficiencies of nutrients during the peri-implantation period and the period of rapid placental development.[2] In general, maternal amino acid concentrations are reduced during pregnancy, especially in the first trimester, presumably reflecting the endocrine changes associated with pregnancy and are returned to normal level within 1 or 2 days after delivery.[3,4] Previous studies have occasionally reported differences in maternal amino acid concentrations in pathologic pregnancies, such as intrauterine growth restriction (IUGR) and diabetes mellitus.[5-8] Placenta surface area and amino acid uptake are reported to be decreased in human and experimental animal models of IUGR.[9] Therefore, it

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is possible that the differences in the maternal protein concentrations could represent an inadequate adaptation to pregnancy and be one of the first changes to occur in pregnancies complicated by IUGR.

Several serum proteins such as albumin, prealbumin, transferrin, and retinol-binding protein have been suggested as sensitive indicators of nutritional status and have been used as clinical indices of intrauterine growth.[10] Prealbumin is a protein that has been proposed as a biochemical marker of energy and nutrient sufficiency in neonates, children and adults.[11,12] This protein is synthesized by the liver and circulates with the retinol-binding and retinol-carrier protein complex.[13] Its short half-life of 2 days is a valuable feature for the estimation of recent changes in protein intake.[13] Furthermore, prealbumin levels have been shown to correlate with patient outcomes and shown to be an accurate predictor of patient recovery in patients who are critically ill and those with chronic disease.[14]

During pregnancy, however, prealbumin, or transthyretin, shows little changes or at most rises slightly in maternal serum.[10,15] Previous studies have shown that the concentration of cord blood prealbumin is lower in premature than in full-term infants, and in full-term infants when compared to adults.[16-19] In the rat is has been shown that placental transfer of prealbumin occurs early in gestation, with fetal synthesis beginning later.[20] However, in human, the origin of prealbumin in human fetal serum remains speculative. There are reports both in support of significant and of poor relationship of prealbumin concentrations between paired cord-maternal serum and fetal birth weight.[16-19,21-23] In the amniotic fluid, the ratio of prealbumin concentrations decreased from the 16th week of pregnancy to term in contrast to its rising trend in cord blood.[24] Lolis et al. reported higher amniotic fluid levels of prealbumin in second trimester IUGR fetuses, and other fetuses with severe malformation or intrauterine deaths.[24]

We hypothesized that serum levels of prealbumin could serve as a marker by which we could identify pregnant women at increased risk for IUGR. The current study was undertaken to (a) monitor the changes in maternal serum prealbumin level throughout normal pregnancy as gestational age increases; (b) to compare the paired maternal serum and cord blood prealbumin level in pregnant women carrying isolated IUGR fetuses in comparison to normal pregnant women; (c) to determine whether maternal serum prealbumin levels could be used as a biochemical marker for intrauterine growth restriction.

Materials and Methods

1. Subjects of the study

Data reported in this study are from patients who received continuous antenatal care and underwent either normal spontaneous vaginal delivery or cesarean section at our institution from January of 2005 until December of 2006. The criteria for eligibility were as follows: (1) well established gestational age confirmed by ultrasonography early in pregnancy, (2) singleton fetus, (3) no fetal anomaly, (4) nonsmoker, (5) normal response to glucose tolerance testing, (6) no evidence of recent infection, (7) no prescribed medications, (8) no maternal medical complications, and (9) no placental pathology such as placenta previa or abruptio placentae. Furthermore, none of the patients received corticosteroid which is known to influence the level of many nutrients. Each patient was examined monthly in the outpatient department until the 28th week of gestation, then bimonthly until the 36th week of gestation and subsequently weekly until delivery. If the women developed any complications throughout the pregnancy, with the exception of IUGR, they were excluded from the study.

Clinical characteristics of the pregnant women in this study are summarized in Table 1. The maternal body mass

index (BMI), a measure of obesity, was calculated with the formula: weight (kg)/height (m)^2, using the pre-pregnancy weight. Appropriate for gestational age (AGA) was defined as fetal growth within the 10th and 90th percentile of reference values for fetuses of similar gestational age.[25] The normal pregnant women were divided into 3 groups according to trimester for comparison: The three groups were as following: Group I-from 5 to 14 gestational weeks [n=25]; Group II-from 15-28 gestational weeks [n=20]; and Group III-from 29-40 gestational weeks [n=25]. Groups I, II and III delivered at term with AGA babies. Intrauterine growth restriction (IUGR) was defined as in utero measurement of estimated fetal birth weight below the 10th percentile of reference values for fetuses of similar gestational age and confirmed at birth if the neonatal weight was less than 10th percentile of reference values for fetuses of similar gestational age.[25] The IUGR group (n=15) consisted of pregnant women with isolated cases of IUGR. All mothers participating in this study gave written informed consent before cord blood sampling.

2. Sample Analysis

The maternal serum and umbilical cord blood samples were collected in the delivery room at birth. The specimens were centrifuged immediately and stored at -80℃ until further analysis for prealbumin. Maternal serum concentrations and cord blood prealbumin concentrations were measured by immunoturbidimetric assay with an automatic analyzer Cobas Integra 400 (Roche Analytical Instruments Inc., Nutley, NJ) according to the methodologies described previously.[26,27] The minimum detectable concentration is 9.5 mg/L.

3. Statistical Analysis

Data are shown as median±SEM except when otherwise noted. Statistical analysis of the results was carried out using the one-way ANOVA for comparison between the three AGA groups divided according to trimester. Multiple regression analysis was performed to evaluate the inde-

Table 1. Clinical characteristics of mothers and neonates

	Parameter	Normal gestation (n=25)	IUGR gestation (n=15)	P value
Mothers	Age (years)	30.8±4.4	28.8±4.8	0.31
	Pre-pregnancy BMI (kg/m^2)	19.6±1.9	19.1±2.7	0.61
	Weight gain (Kg)	13.0±2.2	9.5±5.0	0.06
	Parity (%)			
	Multiparity (%)	57.1	40	
	Primiparity (%)	42.9	60	
	Gestational age at delivery (wks)	39.2±0.7	39.0±2.0	0.72
	Delivery mode			
	Cesarean section (%)	36	40	
	Vaginal delivery (%)	64	60	
Neonates	Birth weight (g)	3166±192	2446±464	0.0007
	Sex			
	Male (%)	56	46.7	
	Female (%)	44	53.3	
	Biparietal diameter (cm)	9.5±0.3	9.0±0.3	0.001

Data represented as mean±STD value.
Significant difference considered as $p < 0.05$.

pendent effects of variables in prealbumin levels. To compare the normal gestation and IUGR group, paired student *t*-test was used. Differences were considered significant at $p<0.05$.

Results

The clinical description of the participants in this study is given in Table 1. Changes in the maternal serum prealbumin levels during normal gestation are shown in figure 1. The median maternal serum prealbumin in 1st, 2nd, and 3rd trimester were as following; 24.4±6.9 mg/dL, 25.1±7.6 mg/dL, and 18.2±9.9 mg/dL, respectively. The maternal serum prealbumin level of 3rd trimester was significantly lower than that of 1st and 2nd trimester.

At 3rd trimester, the maternal serum prealbumin level of the control group and the IUGR groups were 18.2±9.9 and 18.0±5.1, respectively, without any significance difference between both groups ($p=0.89$) (Table 2). Furthermore, there were no significant difference between the cord blood prealbumin level of the control and IUGR group ($p=0.23$) (Table 2).

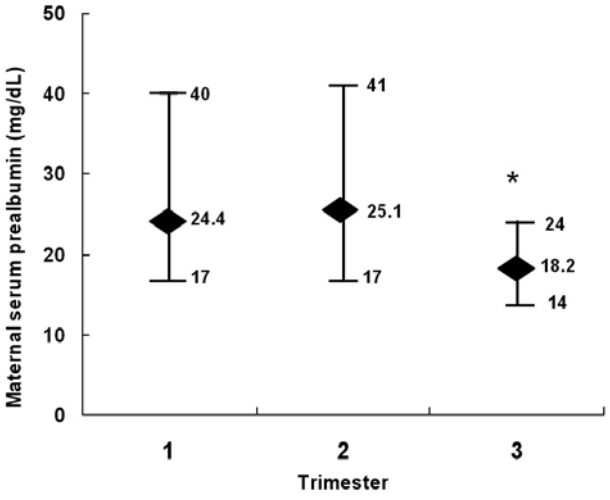

Fig. 1. Changes in maternal serum prealbumin level during normal gestation.
*p < 0.05 vs. 1st and 2nd trimester. Data represented as median±SEM.

Figure 2 presents the relationship between third trimester maternal serum prealbumin level and fetal birth weight (Fig. 2a) and third trimester cord blood prealbumin level and fetal birth weight in normal and IUGR pregnancies (Fig. 2b). There was no significant relationship between

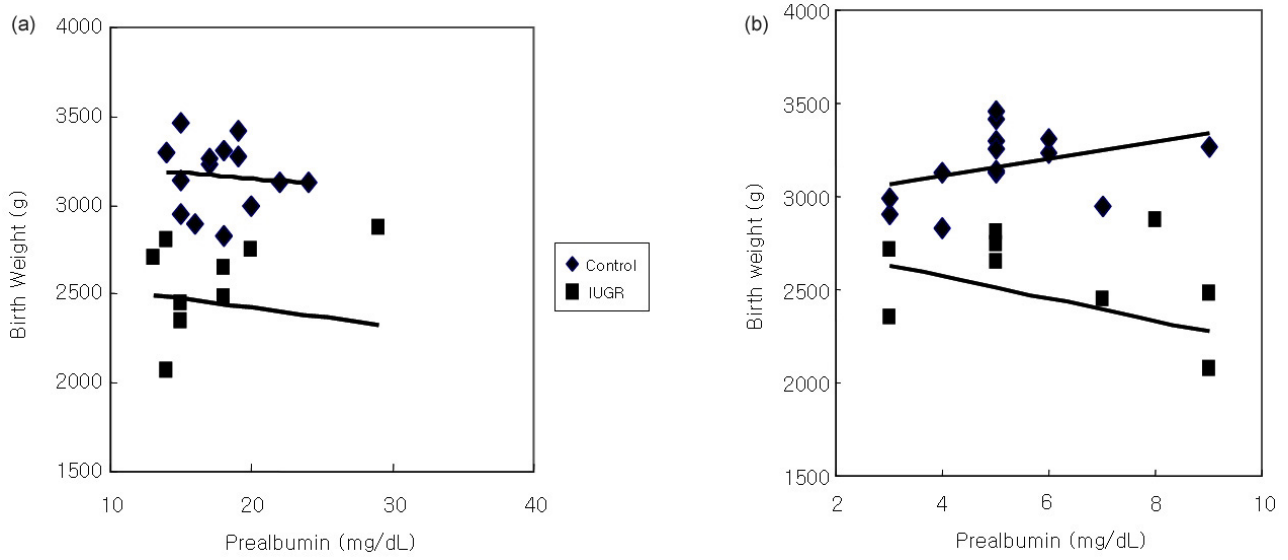

Fig. 2. Relationship between third trimester (a) maternal serum prealbumin level and birth weight in normal (◆; $n=25$; $r=-0.09$; $p=0.74$) and IUGR pregnancies (■; $n=15$; $r=-0.12$; $p=0.75$) and (b) cord blood prealbumin level and birth weight in normal (◆; $n=25$; $r=0.37$; $p=0.19$) and IUGR pregnancies (■; $n=15$; $r=-0.29$; $p=0.42$).

Table 2. Prealbumin level of maternal serum and cord blood from normal and IUGR pregnancies in third trimester

	Normal gestation (*n*=25)	IUGR gestation (*n*=15)	*P* Value
Maternal serum prealbumin	18.2±9.9	18.0±5.1	0.89
Cord blood prealbumin	5.1±1.1	6.1±2.2	0.23

Data represented as median±SEM. Significant difference considered as $p < 0.05$.

fetal and maternal level of prealbumin and fetal birth weight for both normal and IUGR pregnancies.

Discussion

Pregnancy is characterized by a number of endocrine and metabolic adaptations that are necessary for normal growth of the fetus. Several serum proteins such as albumin, prealbumin, transferrin, and retinol-binding protein have been suggested as sensitive indicators of nutritional status and have been used as clinical indices of intrauterine growth.[10] Especially, due to its short half life, prealbumin has been shown to be a sensitive measure of protein and calorie intake in the neonates.[11,30] We expected in our study that variation in the concentration of maternal serum and/or fetal cord blood prealbumin would help predict some of the variation in birth weight, and perhaps identify a subset of fetuses who were destined to be growth restricted.

However, our study failed to demonstrate any difference between maternal serum and cord blood prealbumin levels of normal pregnant women with AGA fetuses and those with isolated IUGR fetuses during third trimester. In an attempt to understand our failure to demonstrate the expected relationship, we first compared our median and lowest serum prealbumin values of normal pregnant women to those published for nonpregnant women.[31] Compared with nonpregnant women, the median value for maternal serum prealbumin level of control group was very close to the lower limit of the normal ranges, while the serum prealbumin values within the lowest quartiles were generally below the published lower limits for normal nonpregnant women (17.8-45.0 mg/dL). The fact that there is no consistent decrease in birth weight in infants born to women with the lowest quartile level of prealbumin in the control group suggests that serum prealbumin levels below the normal ranges for nonpregnant women did not have any adverse effect on birth weight. These findings suggest that standards for nonpregnant adults should be applied cautiously during pregnancy.

Furthermore, control of growth in the fetus and neonate is complex. Several hormones, such as insulin, IGFs, IGFBPs, leptin, and cytokines, have been individually shown to play important roles in regulating fetal growth and nutritional status.[32] Previous reports on the highly complex interactions between the concentrations of various proteins such as retinol binding protein, vitamin A, and albumin with prealbumin and other measures of nutritional status may help explain why we were able to define any significant relationship between prealbumin levels and birth weight.[10]

In addition, this poor correlation between the maternal serum and cord blood prealbumin levels and fetal birth weight may be explained by the fact that body weight is influenced by alterations in body fluid status as well as increase in body mass index.[28] Factors other than nutritional intake may affect serum prealbumin production or degradation. The administration of glucocorticoids or endogenous production of other stress hormones is reported to produce an increase in prealbumin concentration.[29,33]

In the present study, no significant correlation between the maternal serum prealbumin concentration and gestational

age in normal pregnant women was shown. The decrease in maternal serum prealbumin concentrations during third trimester seen in our study here has been reported previously in some studies and is still controversial, but is generally thought to reflect volume expansion with suppression of prealbumin synthesis in the liver by various hormone concentrations.[34]

A number of limitations in the present study should be noted. First, instead of dividing the participants into three different groups according to trimester, the maternal serum prealbumin level should be prospectively measured from the same set of normal pregnant women from early 1st trimester to delivery. Second, further prospective research with larger sample size is needed in order to accurately determine the strength of the relationship between prealbumin and birth weight.

In conclusion, maternal serum and cord blood prealbumin level was not an independent predictor of birth weight or fetal growth restriction. The failure to demonstrate a positive relationship may be due to the complex physiologic changes associated with pregnancy, including plasma volume expansion, and pregnancy related effects on protein biosynthesis in the liver. The lack of association suggests that even if a relationship were identified with increased sample size, the strength of the relationship needs to be reevaluated to assist in the routine clinical management of growth restricted fetuses.

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「국문초록」

목적: 혈청의 prealbumin은 영양 상태를 평가하는 데 있어서 민감한 지표로 사용되며, 측정이 쉽고, 체내의 필수 아미노산의 상태를 잘 반영한다고 알려져 있다. 본 연구에서는 산모의 영양 상태를 평가하는 지표로 prealbumin을 선정하여 일차적으로 산모 혈청내의 prealbumin과 임신 제태연령과의 상관관계를 평가한 후, 산모 혈청 및 태아 제대의 prealbumin과 자궁내 발육 지연과의 상관관계를 분석하고자 하였다.

연구 대상 및 방법: 2006년 1월부터 2007년 12월까지 연세의료원 산부인과를 방문한 산모 중 자궁 내 발육 지연이 초음파상으로 확인된 산모 15명과 정상 대조군 25명을 대상으로 하였다. Prealbumin을 immunoturbidmetric assay를 통하여 정량하여 자궁 내 발육 지연 산모의 혈청 및 태아 제대의 농도를 대조군과 비교함으로써 영양 상태가 태아의 발육에 미치는 영향에 대하여 분석하였다.

결과: 정상 임신 기간 동안 혈청 prealbumin 농도는 재태 주령과 유의한 상관관계가 없었으나 임신 제 3 삼분기 혈청 prealbumin 농도는 제 1, 2 삼분기보다 유의하게 낮았다. 제 3 삼분기에서 태아발육 지연이 있는 군에서의 혈청 및 제대 prealbumin 농도는 대조군과 유의한 차이가 없었으며, 두 군 모두에서 혈청 및 제대 prealbumin 농도는 출생체중과 유의한 상관관계가 없었다.

결론: 산모의 혈청 및 태아 제대 prealbumin 값은 태아의 체중 및 발육지연의 정도와 밀접한 관련이 없는 것으로 사료된다.

중심단어: 영양학적 지표인자, prealbumin, 자궁 내 발육 지연