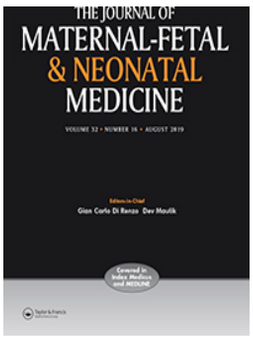

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ORIGINAL ARTICLE

Maternal serum advanced glycation end products level as an early marker for predicting preterm labor/PPROM: a prospective preliminary study

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ABSTRACT

Objective: To evaluate the value of maternal serum advanced glycation end products (AGEs) level at 11–13 weeks' gestation for the prediction of preterm labor and or preterm premature rupture of membranes (PPROM).

Materials and methods: This prospective cross-sectional study is performed in a university-affiliated hospital between February and April 2016. The participants of this study are low-risk pregnant women. Blood samples for maternal AGEs level were collected in the first trimester of pregnancy and all women completed their antenatal follow-up and delivered in our center. During the follow-up 21 women developed preterm labor/PPROM. The first trimester maternal AGEs levels of preterm labor/PPROM cases were compared with uncomplicated cases ($n = 25$) matched for age-parity and BMI. The predictive value of AGEs levels for preterm labor/PPROM was also assessed.

Results: First-trimester AGEs levels were significantly higher in cases complicated with preterm labor/PPROM (1832 (415–6682) versus 1276 (466–6445) ng/L, $p = .001$ and 1722 (804–6682) versus 1343 (466–6445) ng/L, $p = .025$). According to receiver-operating characteristic curve analysis, the calculated cut off value of AGEs was 1538 ng/L with the sensitivity 91.7%, specificity 73.8%; and the negative and positive predictive values were 91.6% and 29.5%, respectively.

Conclusions: For the prediction of preterm labor/PPROM, the relatively high AGEs levels in the first trimester might be a useful marker.

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Preterm labor; advanced glycation end product; pregnancy; first trimester

Introduction

Advanced glycation end products (AGEs) are heterogeneous molecules formed from nonenzymatic and non-oxidative covalent attachment of glucose molecules to target proteins, lipids, and nucleic acids. This post-translational modification is called "glycation" or "Maillard reaction". Glycoxidation refers to the radical-mediated oxidation reaction of both free and protein-bound sugars [1]. The initial product of this reaction leads via reversible Schiff-base, which spontaneously rearranges into and Amadori products, as is the case of the well-known hemoglobin A1C. A series of subsequent oxidation and dehydration, called AGEs are formed. The formation of AGEs is irreversible, and causes a resistant protein deposition to protease [2]. Such AGEs are not formed solely from carbohydrate metabolism but can also result from lipid oxidation and degradation [3]. sNε (carboxymethyl) lysine (CML), pentosidine, and methylglyoxal-derived hydroimidazolone are examples of well-known and widely studied AGEs [4–7].

AGEs play a significant role in the pathogenesis of ageing, diabetic vascular and renal complications, formation and progression of atherosclerosis, and Alzheimer's disease. The glycation of plasma proteins leads to altered structure and function, as in cellular matrix, cell basal membranes, and vessel-wall components [2]. This is initiated by its binding to cell membrane-specific receptors via RAGE, a multiligand transmembrane receptor of the immunoglobulin superfamily [8–10]. AGE–RAGE interactions result in inflammation, oxidative stress, vascular hyperpermeability, enhanced thrombogenicity, and reduced vasorelaxation, causing homeostatic disturbance of the vasculature [11]. Oxidative disorders and inflammation are associated with adverse pregnancy outcomes such

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as gestational diabetes, preeclampsia, preterm labor, preterm premature rupture of membranes (PPROM), intrauterine growth restriction, and oligohydramnios [12–15].

Recent studies in the literature focused on AGEs levels in gestational diabetes, and preeclampsia. The data obtained from these studies showed that increased AGEs levels could lead to the expression of inflammatory cytokines, oxidative stress, and endothelial dysfunction in second trimester [16–19]. However, the data about the role of AGEs levels in preterm labor/PPROM is lacking in the literature. Therefore, the aim of this study was to evaluate the maternal serum levels of AGEs at the first trimester of pregnancy in order to clarify the potential role for subsequent development of preterm labor/PPROM.

Materials and methods

Patients and sampling

This prospective, case-control study included consequently pregnant women who attended their routine antenatal follow-up at 11 and 13 weeks of gestation at a university affiliated hospital between February and April 2016 ($n = 285$). Local institutional review board of the same hospital approved the study (No. 7/January 2016), and informed consent was taken from the participants. Exclusion criteria were multiple pregnancies, history of preterm delivery or PPROM in previous pregnancies, presence of chronic diseases diagnosed before conception (hypertension, thyroid dysfunction, diabetes, and renal or liver disease), and current pregnancies diagnosed with gestational diabetes and preeclampsia. All of the subjects were nonsmokers. Blood samples from mothers were immediately centrifuged, and serum was separated and stored at $-80\,^{\circ}C$ in the first trimester of pregnancy for screening purposes. AGEs levels were measured by an autoAnalyzer (ChemWell 2910, Awareness Technology, FL, USA) by a commercially available kit by enzyme-linked immune sorbent assay (ELISA) based on biotin double antibody sandwich technology.

The last menstrual period and fetal crown-rump-length on early ultrasound were used for estimation of the gestational age. Maternal height and weight were measured at enrollment to the study and body mass index (BMI) was calculated as weight (kg)/height (m^2). Mode of delivery, gestational complications as preterm labor, and PPROM during the gestation or delivery were noted. Preterm labor was defined as delivery before 37 completed gestational weeks [20], and PPROM was defined as rupture of membranes before the onset of labor [21]. The clinical outcome of each fetus was evaluated after birth, and neonatal intensive care unit (NICU) admissions were recorded.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences version 17 software. Normality of the continuous variables was tested by Kolmogorov–Smirnov test. Continuous data are expressed as mean standard deviation and were analyzed with two-independent sample tests. Chi-square and Fisher's exact tests were used for categorical data. Correlation between numerical variables was tested with Pearson's correlation test when parametric test assumptions were met and with Spearman's correlation coefficient when those assumptions were not met. Area under the curve (AUC) and 95% confidence interval (CI) for each obstetric complication were evaluated by receiver operating characteristic (ROC) analysis. The best cutoff point of AGEs and diagnostic performance such as sensitivity, specificity, and positive and negative predictive values were calculated. The significance boundary was given as .05.

Results

During the study period, 285 healthy low-risk pregnant women in the first trimester fulfilled the inclusion criteria. Thirty-three cases dropped out due to fetal congenital anomaly, abortion or lost to follow-up. Two hundred fifty-two subjects continued antenatal follow-up during the study period. Among these, 21 women subsequently developed preterm labor/PPROM. The controls were matched for age, parity, and BMI who had uncomplicated pregnancies that ended in live birth ($n = 25$). The characteristics of the study population are presented in Table 1. No difference was found in the gestational age at sampling when complicated and noncomplicated cases are compared (11.61 ± 0.66 versus 12 ± 0.59 weeks, $p = .096$).

Preterm labor occurred in 21 (8.3%) patients, and PPROM in 9 (3.5%) patients. Among the participants of the study, 63% ($n = 29$) delivered vaginally, and cesarean section was required in 37% ($n = 17$). Mean gestational age at birth and birth weight of the neonates was 38.5 ± 1.7 weeks and 3246 ± 500 g, respectively. AGEs levels in cases and controls, and levels regarding the mode of delivery are given in Table 2. There was no statistically significant difference between nulliparous women and parous women in terms of AGEs levels (1406 (707–2148) ng/L versus 1398 (466–6684) ng/L, $p = .737$).

Table 1. Demographic characteristics of the study population.

Variables	Mean ± SD
Age (years)	28.7 ± 5.62
Gravidity[a]	2 (1–8)
Parity[a]	1 (0–4)
BMI (kg/m^2)	27.86 ± 3.62
Gestational age at birth (week)	38.53 ± 1.78
Birthweight (kg)	3246 ± 500
AGEs (ng/L)[a]	1.40 (0.46–6.68)

[a]Variables are median (Min–Max).
BMI: body mass index; AGEs: advanced glycation end products.

Table 2. AGEs levels of in subgroups of patients.

Variables	**AGEs** levels (ng/L)	*p*
Preterm labor		.001*
Yes (21)	1832 (415–6682)	
No (25)	1276 (466–6445)	
PPROM		.025*
Yes (9)	1722 (804–6682)	
No (37)	1343 (466–6445)	
Delivery type		.529
NVD (29)	1395 (466–6075)	
CS (17)	1577 (707–6682)	
NICU admission		.097
Yes (7)	1864 (707–6682)	
No (38)	1371 (466–6445)	

NVD: normal vaginal delivery, C/S: cesarean section; PPROM: preterm premature rupture of membranes; NICU: neonatal intensive care unit.
*$p < .05$, significant.

Maternal AGEs levels [median (min-max)] were significantly higher in cases complicated with preterm labor and PPROM compared to uncomplicated gestations [1832 (415–6682) versus 1276 (466–6445) ng/L, $p = .001$, and 1722 (804–6682) versus 1343 (466–6445) ng/L, $p = .025$]. Seven (15%) neonates required NICU admission and there was no statistically significant difference in AGEs levels of mothers of fetuses with or without NICU admission [1864 (707–6682) versus 1371 (466–6445) ng/L, respectively, $p = .097$].

According to the Spearman rank correlation analyses, the age, BMI, and parity were not correlated with maternal AGEs levels ($r = -0.213$, $p = .122$; $r = -0.196$ $p = .156$; $r = -0.05$, $p = .722$, respectively). The predictive accuracy of AGEs early in gestation as a marker for preterm labor and/or PPROM was found by ROC analysis [AUC 0.82, 95%CI 0.71–0.93, $p = .001$]. The best cut-off point for AGEs and diagnostic performance such as sensitivity, specificity, and positive and negative predictive values were also calculated. An AGEs threshold of 1538 ng/L had a sensitivity of 91.7%, specificity of 73.8%, negative predictive value of 91.6%, and positive predictive value of 26.9%.

Discussion

Advanced glycation end products are reactive derivatives of nonenzymatic glycation reactions between glucose and proteins, lipids, and nucleic acids. Aging also causes physiological formation of AGEs in tissues, but this is a relatively slow and less harmful process. However, the formation of AGEs dramatically increases under high-glucose condition. Recently, some studies demonstrated that increased level of AGEs has been associated with poor prognosis in gestations, where complicated pregnancies such as gestational diabetes, and preeclampsia, involving endogenous inflammation and oxidative stress are reported [16–19]. The present study aimed to evaluate the value of first trimester AGEs levels in a group of pregnant women, including preterm labor, and PPROM. The analysis revealed that high levels of first-trimester AGEs levels were associated with preterm labor and PPROM later in gestation.

Preterm labor is a significant public health challenge associated with high levels of neonatal morbidity and mortality and long-term health effects. Preterm birth is a global issue that continues to rise worldwide. The most recent data show that the incidence of prematurity in the USA has increased from 12.3% in 2003 to 12.7% [22]. But, there is still no universally accepted screening marker that can detect this complication before its onset. Most clinical and research evidences show that a number of possible etiologies can lead to final common pathway, resulting in spontaneous preterm labor. Preterm deliveries can be medically indicated/elective procedures or they can occur spontaneously. Spontaneous preterm labor is commonly associated with intrauterine infection/inflammation. Exaggerated inflammatory reaction can lead to membrane rupture as a result of decidual or membrane activation and may be initiated long before preterm labor or PPROM are clinically evident. Elevated levels of proinflammatory mediators, cytokines, and proteases have been demonstrated in the amniotic fluid of women with preterm labor and these factors may cause the dissociation of extracellular matrix [23–25]. PPROM occurs 3–4% of all pregnancies and precedes 40–50% of all preterm births. It causes a significant proportion of neonatal morbidity and mortality [26]. Therefore, a first-trimester marker may aid in the prediction of this complication and improve management of such cases.

This is the first study demonstrating the probable value of first trimester AGEs for the prediction of preterm labor and PPROM risks. Previous studies showed the role for AGEs in the overexpression of intracellular reactive oxygen species (ROS), impairs proteasomal activities, and inflammatory responses [7,27,28]. AGEs may give rise to tissue damage both directly, and indirectly, by binding to RAGE, which is secreted from

many cell surfaces, such as macrophages, monocytes, endothelial cells, neurons, and smooth muscle cells. This interaction results in oxidative stress, expression of genes of cytokines such as TNF alpha, IL-1beta, and IL-6, NF-kappaB activation, chronic inflammatory responses, and cellular and vascular dysfunction. Thus, RAGE ligands and subsequent signaling might initiate uterine contractility, cervical maturation, and PPROM [29–31].

The mean fasting serum levels of AGEs is highly variable, ranging from 3.59 to 13.53×10^3 μg/mL in healthy people [32]. Little is known about serum AGEs levels in pregnant women. Chen et al. showed that in the last trimester in maternal blood, the concentrations of the AGEs were significantly higher in the preeclampsia group than in controls, and the level of AGEs in controls was between 400 and 450 ng/L [18]. In the recent literature, Yang et al. found that mean AGEs level in a healthy pregnancy in the early third trimester is 606.26 ± 111.12 ng/L and 518.04 ± 173.24 ng/L in the late third trimester [33]. To the best of our knowledge, there is no data regarding the cut-off levels of AGEs in the first trimester for prediction of subsequent development of gestational complications. This is the first study evaluating maternal serum AGEs level at 11–13 weeks' gestation for the prediction of preterm labor and/or PPROM. Our study showed that in the first trimester the serum AGEs levels was significantly higher in the preterm labor group than in healthy controls [1832 versus 1276 ng/L, $p < .001$, respectively]. We found that with a cut off value of 1538 ng/L, sensitivity of AGEs for preterm labor and PROM was 92.8% and specificity was 73.9% with a negative predictive value of 91.6% and a positive predictive value of 29.5%. This high sensitivity and relatively low specificity indicates that first trimester maternal serum AGEs levels might be useful in the prediction of preterm labor/PROM. However, our sample size was limited, and the findings must be verified in larger populations.

In conclusion, AGEs regulates a number of pivotal processes such as inflammation, apoptosis, proliferation, and autophagy. Oxidative stress and ROS production, based on the AGEs hypothesis, may potentially benefit from the restriction of AGEs on diet as a nonpharmacologic intervention, the use of natural inhibitors or antioxidant treatment such as vitamin C, E [16,34–37]. Thus, reduction of inflammation might help to decrease the level of induced damages. Development of therapeutic strategies to block AGEs/RAGE may be hopeful in future adverse pregnancy outcomes such as preterm labor and PPROM.

Disclosure statement

No potential conflict of interest was reported by the authors.

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