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Case Report

Second trimester amniotic fluid uric acid, potassium, and cysteine to methionine ratio levels as possible signs of early preeclampsia: A case report

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ABSTRACT

Objective: The precise etiopathogenesis of preeclampsia (PE) still remains enigmatic. In recent published work, there is a scientific trend aiming to unveil early biomarkers of PE based on amniotic fluid compositional changes before the development of clinical symptoms.**Case Report:** We describe a case of an apparently clinically healthy woman, whose amniotic fluid, retrieved after amniocentesis at 22^{2/7} gestational week, had elevated uric acid and potassium concentration, as well as cysteine to methionine ratio. At the time of amniocentesis, conventional clinical signs of PE were absent. The woman developed severe PE and intrauterine growth restriction, at the 28^{0/7} week of gestation.**Conclusion:** Although the limitation of such studies lies in the fact that amniocentesis is an invasive procedure, and thus employed only under specific indications, our scientific observations might be useful for future research towards unraveling the causes of PE.Copyright © 2016, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Preeclampsia (PE) is a common, potentially life-threatening pregnancy disorder, characterized by *de novo* hypertension and proteinuria. Since the precise etiopathogenesis of PE has not yet been fully elucidated, there is a steady increase in studies seeking to identify potential biomarkers for early detection of women destined to develop PE [1–6]. Most of the scientific publications [1,3,5] follow the conventional approach by determining PE biomarkers in maternal blood or urine. However, since PE is considered a syndrome of multifactorial origin, an intriguing possibility,

which has gained ground lately, is to investigate patterns of metabolites in amniotic fluid (AF) retrieved for the purposes of genetic analysis [2,4,6].

In this study, we present a case of a woman who developed PE at the 28^{0/7} week of gestation. Her AF retrieved at the 22^{2/7} week had elevated uric acid and potassium concentration, as well as cysteine to methionine ratio. To the best of our knowledge, there are no available data on AF methionine cycle metabolites and potassium levels in preeclamptic women.

Case Presentation

The case described in the present report was incidentally observed during our previous studies [7,8] sought to explore AF composition in relation to maternal and fetal characteristics, as well as birth outcome. A 31-year-old nulliparous woman, without any previous medical history, was referred for a Level II ultrasound. The

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examination revealed a fetus with normal anatomy and measurements consistent with the dates, except of the femoral and humeral length that were at the 5th centile for the given gestational age. Due to these sonographic markers associated with chromosomal abnormalities, the woman underwent amniocentesis at the 22^{2/7} week of gestation that revealed a normal fetal karyotype.

As a standardized procedure in the frame of our research, informed consent was obtained from the woman and an aliquot of her AF was analyzed to determine the concentrations of the compounds of interest. The experimental protocols followed are described in our previous publications [7,8]. The procedures were in accordance with the ethical approval attained by the Bioethics Committee of the Medical School, Aristotle University, Thessaloniki, Greece (A19479–26/2/08).

To present her abnormal/extreme values for uric acid, potassium, and cysteine to methionine ratio, against the mean values recorded in our previous studies [7,8], two methodological approaches were adopted. At first, box plots of raw data were created in SPSS v.15.0 statistical software (SPSS Inc., Chicago, IL, USA). Secondly, the woman's raw data for uric acid, potassium, and cysteine to methionine ratio were transformed to z-scores using the mean and standard deviation of pregnant populations from previous studies [7,8]; z-scores > 3, in absolute value, were considered extreme outliers.

The woman had an extremely high AF uric acid concentration (6.69 mg/dL), compared to the average value referred to in the literature (3.62 ± 0.74 mg/dL, $n = 52$ [8]), as indicated in Figure 1A and confirmed by the extreme uric acid z-score [$z\text{-score}_{\text{uric acid}} = (6.69 - 3.62)/0.74 = 4.15$]. Potassium concentration (4.25 mmol/L) was also high compared to the average value (3.47 ± 0.28 mmol/L, $n = 52$ [8]) and, according to the z-score [$z\text{-score}_{\text{potassium}} = (4.25 - 3.47)/0.28 = 2.78$], the woman was considered an outlier (Figure 1B). Cysteine to methionine ratio (3.30) was high compared with the mean value (1.50 ± 0.54 , $n = 78$) calculated from our previous study [7] (Figure 1C) and the woman was marked as an extreme outlier based on her z-score [$z\text{-score}_{\text{cys/met}} = (3.30 - 1.50)/0.54 = 3.33$].

At the 28^{0/7} week of gestation, she developed hypertension (145/90 mmHg) and all fetal measurements were found to be below the 10th centile for gestational age. She was transferred to a tertiary fetal-maternal care unit and, 3 days later, she developed severe PE with 24-hour urine collection protein excretion of 6190 mg. Her serum uric acid, at the time of admission, was 5.8 mg/dL and increased progressively in the following 2 days to 6.22 mg/dL. She gave birth to a female newborn, weighing 870 g. After delivery, the patient developed bilateral pleural effusion, which was managed conservatively.

Discussion

Among different biomarkers of PE, uric acid concentrations in maternal blood have been of specific interest. Hyperuricemia is a common clinical characteristic in 75% of preeclamptic pregnancies and, according to Bainbridge and Roberts [9], increased uric acid levels in PE may originate, apart from maternal organs and vasculature, from the fetus and the placenta, as well. Concerning AF, the data on uric acid levels seem rather controversial [6,10]. In the present preeclamptic case, AF uric acid levels at 22^{2/7} weeks of pregnancy were extremely elevated. This rise in AF uric acid concentration concurs with the observation of Kim et al [10] who found an increased third trimester AF uric acid in women with PE compared to women with normal pregnancy. At a first glance, our observations seem to contradict the findings of a recent study [6]. In fact, Fruscalzo et al [6] reported no statistical significant difference in AF uric acid concentrations between women who developed PE and controls. It must be noted, however, that such a discrepancy may originate from differences in gestational age of AF retrieval, since Fruscalzo et al [6] collected the specimens earlier in the second trimester. In the present case, PE was associated with fetal growth restriction. Uric acid may be involved in pathological cell signaling events, inhibiting fetal growth through several pathways. One possible mechanism is through inhibition of renal endothelial cell proliferation. Another mechanism, probably interrelated with the previous one, is through reducing placental blood flow—by reducing endothelial nitric oxide synthesis—and, therefore, decreasing oxygen and nutrient transfer from maternal to fetal circulation [9,11].

Concerning potassium, it is reported in the literature, that high maternal plasma potassium levels during the first half of pregnancy are associated with higher risk for the development of severe PE [12]. In fetal life, potassium is transported across the placenta from mother to fetus. Therefore, the higher AF potassium levels may ensue from high maternal plasma potassium levels. Aldosterone and potassium homeostasis are of utmost importance for the evolution of pregnancy; however, a critical assessment of our results against published data on the role of potassium levels as marker of PE is not feasible due to the fairly limited scientific data in this area.

The extremely elevated cysteine to methionine ratio may indicate a metabolic perturbation of the methionine cycle. In a case–control study [13], plasma methylation metabolites at delivery were found to be elevated both in maternal and fetal compartments in preeclamptic pregnancies. The role of the conjugated metabolic pathways of methionine and folate is of great importance, during

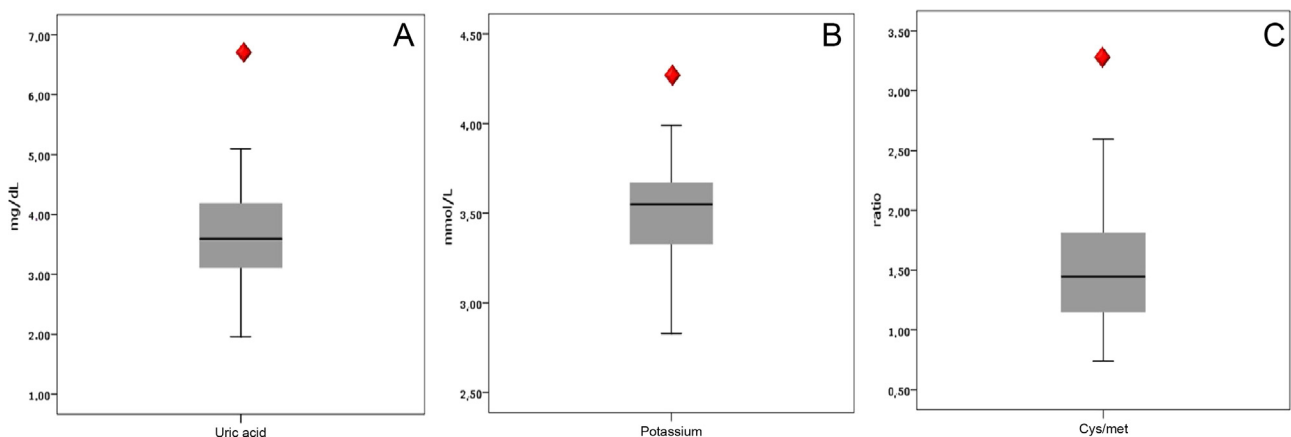


Figure 1. Box plots indicating second trimester amniotic fluid (A) uric acid concentration, (B) potassium concentration, and (C) cysteine to methionine ratio of a woman who developed preeclampsia (rhomb symbol), in comparison to data from normal pregnancies published in previous studies [7,8].

intrauterine life, since they deliver methyl groups for use in critical processes, such as purine synthesis, as well as phospholipid and protein biosynthesis [14]. Monsen et al [15] highlighted this role suggesting that methionine—and the related metabolites and B vitamins—may affect fetal growth and development.

As has already been mentioned, there is a scientific trend aiming to unveil early biomarkers of PE based on AF compositional changes before the development of the clinical symptoms [2,4,6]; this body of work would lend insights into the causes of PE, leading to effective prophylactic interventions that could optimize maternal and perinatal outcomes. Under this prism, our observations might be useful for future research towards exploring PE. It should be remembered, though, that the limitation of such studies lies in the fact that amniocentesis is an invasive procedure, employed only under specific indications.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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