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COMMENT

An elevation in serum uric acid precedes the development of preeclampsia

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A hundred years ago, Slemons et al. first reported that eclamptic patients had higher levels of serum uric acid [1]. Since then, uric acid has been considered a risk factor for preeclampsia [2], and this issue has been intensively investigated. However, the data are inconsistent, and it remains unclear whether uric acid plays a causal role in the later development of preeclampsia. A reason for the inconsistency could be partially attributed to the temporal variation in serum uric acid during pregnancy. In early pregnancy, serum uric acid falls due to the pregnancy-induced expansion of blood volume and the increase in maternal renal blood flow [3]. The uricosuric action of estrogen also reduces the serum concentration of uric acid [3]. In turn, serum uric acid rises to the levels observed in nonpregnant women in later pregnancy because of an increase in fetal uric acid production and a maternal glomerular filtration rate decline [4]. Therefore, we need to be cautious about the timing of uric acid measurements to examine the pathological role of uric acid during pregnancy. In clinical medicine, serum uric acid measurements are often carried out at presentation, at the onset of preeclampsia, and at term, so proper interpretation of uric acid values must include an understanding of the normal physiology of serum uric acid during pregnancy.

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Uric acid is not simply an inert bystander; increasing evidence suggests that it plays several pathological roles in inducing hypertension and kidney disease [2, 5]. Importantly, many of the phenotypes mediated by high uric acid levels are also observed in preeclampsia. Specifically, experimental studies have consistently shown that increasing uric acid can induce endothelial dysfunction, oxidative stress and mitochondrial dysfunction [6]. In the development of preeclampsia, a potential mechanism by which uric acid could be involved is potentiating endothelial dysfunction to disturb spiral artery formation, leading to hypoxia in the placenta (Fig. 1). Trophoblast shedding is also induced by uric acid, contributing to the development of abnormal placentation [7]. Given these facts, uric acid could be a contributor to the pathological process in the early phase of placentation. In fact, recent studies documented that uric acid levels in the first and second trimester likely predicted the later development of preeclampsia [8–10], while some studies showed negative results [11].

In the article of Yue et al. published in this issue of the Journal [12], the authors have addressed the issue as to whether hyperuricemia is associated with the development of preeclampsia and with preeclampsia-related adverse pregnancy outcomes, including preterm delivery, preterm preeclampsia and low birth weight. They performed a retrospective study of 4725 singleton pregnant women, measuring serum uric acid levels before 20 weeks of gestation, and found that the risk of preeclampsia development was positively associated with serum uric acid concentrations. Kaplan–Meier analysis also showed that delivery occurred earlier when the serum uric acid level was higher at 8–12 weeks of gestation [12]. These data suggest that an elevation of serum uric acid (>240 or 300 μM/L, or 4–5 mg/dL) in early pregnancy could be involved in the later development of preeclampsia and preterm delivery.

There are likely several mechanisms driving the increase in serum uric acid in preeclampsia, including renal

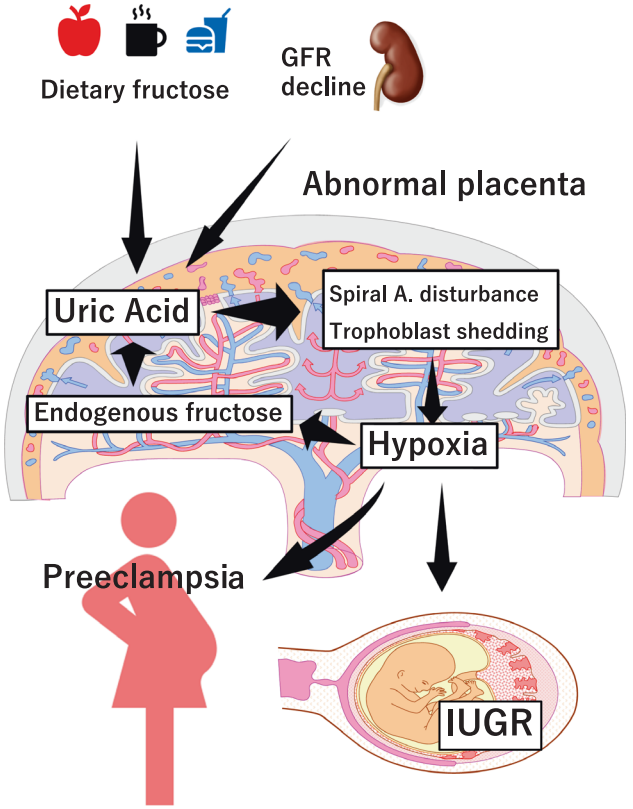

Fig. 1 Uric acid may play a role in the development of preeclampsia. An elevation of uric acid due to either dietary fructose or impaired renal clearance of uric acid disturbs spiral artery formation and causes trophoblast shedding, leading to immature placentation and subsequent hypoxia in the placenta as well as the fetus. Low-grade oxygen drives the development of preeclampsia in the maternal body and intrauterine growth retardation (IUGR) in the fetus, along with endogenous fructose production, which also joins the vicious cycle to accelerate maternal hyperuricemia. GFR glomerular filtration rate

vasoconstriction and the release of fetal DNA into the circulation, which is then degraded in the liver to generate uric acid. [13] However, another likely mechanism, especially before preeclampsia manifests, might be an increase in the placental production of uric acid [14]. Both the placenta and fetus endogenously produce fructose in early pregnancy [15], which is metabolized to produce uric acid as a byproduct. Importantly, this system is conserved not only in humans but also in several types of mammalian species, including dogs, cats and guinea pigs, suggesting that fructose might be required for the physiological process during early pregnancy [15]. During this early period of pregnancy, both the fetus and placenta need to overcome physiological hypoxia until placentation is completed. Fructose is a unique sugar that is metabolized under hypoxia to provide a variety of nutrients [15] and therefore supports the developmental process of the placenta and fetus. However, when fructose is excessive, the process is different. A deleterious effect of excessive fructose is the overproduction of uric acid, which is linked to pathological processes. While excessive fructose can be endogenously produced under sustained hypoxic conditions due to immature placentation, it could also be caused by maternal diet. In fact, maternal sugar intake is a risk factor for the development of preeclampsia and poor fetal outcomes [16, 17]. Diets high in fructose prior to pregnancy might drive hyperuricemia in early pregnancy and predispose women to develop preeclampsia (Fig. 1).

There is clearly increasing evidence of a pathogenic role of elevated uric acid during early pregnancy on placental, fetal and maternal health. Clinicians should consider measuring serum uric acid in early pregnancy as an additional approach to assess potential risk for the later development of preeclampsia, and those with higher levels (>240 or 300 μM) should be followed more closely. We call for more experimental studies to investigate the safety of lowering uric acid in pregnancy on the health of the fetus. In addition, pregnant women should be told to avoid drinking sugary beverages.

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Compliance with ethical standards

Conflict of interest RJJ received an honorarium from Horizon Pharma and has equity with Colorado Research Partners LLC. TN and RJJ also have stock with XORTX therapeutics. DH has no disclosures.

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