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ORIGINAL ARTICLE

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Serum uric acid as a novel marker for uterine atony and post-spinal vasopressor use during cesarean delivery

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ABSTRACT
Introduction: Serum uric acid is a marker for oxidative stress in preeclampsia. Because oxidative stress can result in diminished uterine contractility and impaired vascular relaxation, we hypothesized that an elevated serum uric acid level in women undergoing neuraxial anesthesia for cesarean delivery would be associated with greater uterine atony, as measured by supplemental uterotonic agent use and blood loss, and less hypotension, as measured by total vasopressor use.
Methods: All records of patients ($n = 2527$) undergoing cesarean delivery in 2009 were reviewed. Serum uric acid was measured within 24 h of delivery in 509 patients; data from 345 patients with singleton pregnancies undergoing neuraxial anesthesia were analyzed. Demographic data, medical and obstetric history, anesthetic management and peripartum course were evaluated. ANOVA, Chi-square, and multivariate logistic and linear regression analyses were performed.
Results: Increased serum uric acid correlated positively with preeclampsia and the need for supplemental uterotonic agents (odds ratio 1.53, 95%CI 1.2–2.0, $P = 0.002$), but not blood loss. The presence of preeclampsia also correlated with greater supplemental uterotonic agent use ($P = 0.01$). The correlation between serum uric acid and post-spinal vasopressor use (i.e., none, moderate, and high) was of borderline significance ($P = 0.05$). In patients without diabetes, serum uric acid levels correlated inversely with post-spinal vasopressor use ($P = 0.04$).
Conclusions: Elevated serum uric acid in parturients undergoing cesarean delivery with neuraxial anesthesia correlated with increased use of supplemental uterotonic agents and decreased use of post-spinal vasopressors. Further validation of this study is required to determine if serum uric acid in parturients can serve as a reliable predictor for higher and lower occurrences of uterine atony and spinal-induced hypotension, respectively.

Keywords: Uric acid; Uterine atony; Uterotonic agents; Spinal anesthesia; Vasopressor

Introduction

First reported in the beginning of the 20th century,[1] the association between elevated serum uric acid (UA) and preeclampsia has been attributed to renal dysfunction and the degradation of purines from maternal, fetal or placental tissues.[2] The enzyme responsible for metabolizing purines to UA is xanthine oxidase/dehydrogenase (XO), which produces reactive oxygen species (ROS), such as superoxide and hydrogen peroxide, as by-products.[3] Indeed, oxidative stress is considered an essential contributor to the development and maintenance of preeclampsia,[4] and serum UA has subsequently been proposed as an appropriate marker for the severity of this stress.[5,6]

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Oxidative stress is witnessed in patients with heart failure,[7] for whom an elevated serum UA correlates with depressed myocardial contractility, impaired hemodynamic responses, and increased vascular tone,[8] and serves as an independent predictor of a poor prognosis.[9] In such cases, XO is the major source of elevated UA and ROS.[10] ROS contribute significantly to endothelial dysfunction in cardiovascular disease through inactivating endothelial nitric oxide and impairing vasorelaxation.[11] An elevated UA has been observed to be an independent predictor for the development of hypertension;[12,13] the inhibition of XO with allopurinol has been used successfully in the treatment of hypertension.[14] Of interest, the elevated serum UA and hypertension associated with preeclampsia have a positive correlation during pregnancy and undergo similar normalization times in the postpartum period.[15]

During pregnancy, oxidative stress may be responsible for the impaired relaxation of vascular smooth muscle that results in hypertension, a signature feature

of preeclampsia.[16] The hypertension associated with preeclampsia can exhibit significant resistance to multimodal antihypertensive therapy; even the administration of spinal anesthesia results in less hypotension in preeclamptic than in healthy parturients.[17] By contrast, in the pregnant human uterus, XO produced ROS have been demonstrated to significantly impair the contractility of non-laboring myometrium retrieved at cesarean delivery.[18]

Given these associations between serum UA and ROS levels with reduced uterine contractility and impaired vasorelaxation, we hypothesized that an elevated serum UA level in women undergoing neuraxial anesthesia for cesarean delivery would be associated with impaired uterine contractility, as determined by greater supplemental uterotonic agent use and blood loss, and less hypotension, as measured by less vasopressor use.

Methods

Following Institutional Review Board approval, we conducted a retrospective chart review of all patients who underwent cesarean delivery over a one-year period (1 January 2009 to 31 December 2009) at the Brigham and Women's Hospital. The hospital's database was used to identify all patients undergoing cesarean delivery; this list was independently verified by comparison with an anesthesia quality assurance/postoperative visit database.

Inclusion criteria included all patients with a singleton pregnancy for whom serum UA levels were determined within 24 h of cesarean delivery. No limitations were placed on maternal and gestational age or the urgency of the cesarean delivery. Exclusion criteria included those patients with incomplete medical records, use of general anesthesia, pre-existing coagulation abnormalities or hyperuricemia before pregnancy. The following data were collected: maternal age, maternal body mass index (BMI) on the day of caesarean delivery, gestational age, blood pressure and heart rate on admission, past medical and obstetrical history and use of medications including those which could affect vascular and uterine tone (labetalol, terbutaline and oxytocin). Risk factors for uterine atony including presence of labor, labor augmentation, maternal diabetes (gestational, type I or type II), poly- or oligohydramnios, chorioamnionitis and abnormal placentation were also assessed. Laboratory data were also collected, including serum UA, pre- and postoperative hematocrit and hemoglobin, serum creatinine, platelet count and coagulation profile. In our institution, measurement of serum UA (normal range 2.4–5.7 mg/dL, including pregnancy;[19] a level >6.0 mg/dL during pregnancy is clinically interpreted as being suggestive of preeclampsia[20]) is performed utilizing an automated Olympus system based on modifications of the Fossati method.[21] Indications for cesarean delivery, birth weight, type of neuraxial anesthesia technique, duration of labor before cesarean delivery, intraoperative intravenous fluid therapy, vasopressor use and complications (i.e., transfusion requirement, hysterectomy, Bakri balloon placement, packing, embolization or ligation of blood vessels, and intensive care unit admission) were also recorded.

The diagnosis of hypertension and preeclampsia were based on widely accepted clinical criteria for the diagnosis and categorization[22] and were recorded with the relevant outcomes from the discharge summary. The provision of anesthesia for cesarean delivery in our hospital utilizes a standardized protocol. In brief, an 18-gauge intravenous catheter is inserted, an infusion of lactated Ringer's is started, and baseline standard monitors are applied, with blood pressure measured at 3-min intervals. Spinal or combined spinal-epidural (CSE) anesthesia is administered through a 25-gauge Whitacre (±17-gauge Tuohy needle) using 0.75% hyperbaric bupivacaine 1.6 mL (12 mg) with fentanyl 0.2 mL (10 μg) and preservative-free morphine 0.2 mL (200 μg). The patient is placed supine with left lateral tilt created by a wedge placed under the right hip. A T4 sensory level to pinprick is achieved before surgery commences. Administration of vasopressors is at the discretion of the anesthesiologist, with a basic therapeutic guideline of responding to a 20% decrease in mean arterial pressure or a systolic blood pressure <100 mmHg, including in patients with severe hypertension or preeclampsia. Phenylephrine is the vasopressor of first choice, with ephedrine given primarily when hypotension is accompanied with bradycardia. An oxytocin infusion (30 IU in 500 mL) is started upon delivery of the fetus, with the rate, as well as the need for supplemental uterotonic agents (i.e., intramuscular methylergonovine, carboprost tromethamine, and rectal misprostol), determined by mutual agreement of the obstetrician and anesthesiologist. Upon arrival in the postoperative recovery unit, a standardized regimen of oxytocin 3 IU/h (50 mL/h) is administered via an infusion pump for 5 h.

Statistical analysis

The primary outcome of the study was the presence of uterine atony, as measured by the need for supplemental uterotonic agents in addition to oxytocin in patients with elevated serum UA. The number of patients was determined by assuming a 12% increase in the incidence of obstetric hemorrhage in patients with preeclampsia who are known to have high serum UA compared to controls.[23] The cause of obstetric hemorrhage in 80% of cases is related to uterine atony.[24] Based on these data, we determined the sample size to be 105 patients using a difference in proportions power analysis (power 80%, alpha 0.05). We increased the number of patients in our study to account for our secondary outcome,