Urinary tract infection during pregnancy, angiogenic factor profiles, and risk of preeclampsia

Sarah Rae Easter, MD; David E. Cantonwine, PhD; Chloë A. Zera, MD, MPH; Kee-Hak Lim, MD; Samuel I. Parry, MD; Thomas F. McElrath, MD, PhD

BACKGROUND: Despite decades of research, and much progress in discernment of biomarkers in the maternal circulation, the pathogenesis of preeclampsia (PE) remains elusive. The pathophysiology of PE is believed to involve aberrant placentation and an associated increase in systemic inflammation. In this conceptualization, PE becomes more likely when the level of systemic inflammatory burden inherent in pregnancy itself exceeds the maternal capacity to compensate for this additional stress. If this is the case, then it is possible to hypothesize that conditions, such as infectious disease, that increase systemic inflammatory burden should also increase the risk of PE. As urinary tract infection (UTI) represents a common source of inflammation during pregnancy, we tested whether presence of UTI during pregnancy increased the odds of developing PE. Prior work has documented this association. However many of these studies were limited by small cohort sizes and insufficient control for covariates.

OBJECTIVE: The present study is a secondary analysis of a robust contemporary obstetrical cohort recruited to examine the ability of longitudinally sampled maternal angiogenic concentrations to predict PE. We hypothesize that the occurrence of UTI during a pregnancy is associated with the later occurrence of PE in that pregnancy. As PE is believed to be associated with aberrations in systemic angiogenic levels (placental growth factor and soluble isoform of VEGF receptor), we further hypothesize that there will be significant interactions between maternal angiogenic protein levels and the occurrence of UTI.

STUDY DESIGN: Women aged ≥18 years (n = 2607) were recruited and followed up prospectively from the initiation of prenatal care through delivery at 3 regional academic centers. PE was defined by American Congress of Obstetricians and Gynecologists criteria and was independently validated by a panel of physicians. UTI was defined by the presence of clinical symptoms necessitating treatment in addition to supportive laboratory evidence. Multivariate logistic regression models were used and controlled for maternal age, race, parity, body mass index, hypertension, diabetes, in vitro fertilization, and smoking status.

RESULTS: There were 129 women with diagnosed UTIs and 235 with PE. Patients with UTI in pregnancy had higher rates of PE (31.1% vs 7.8%, P < .001) compared to those without reported UTI. The mean gestational age (SD) for UTI diagnosis in PE cases and controls was 25.6 (10.4) and 21.9 (10.9) weeks, respectively (P = .08). The unadjusted odds ratio for PE in the setting of UTI was 5.29 (95% confidence interval, 3.54–7.89). After controlling for confounders, UTI was associated with an odds ratio for PE of 3.2 (95% confidence interval, 2.0–5.1).

CONCLUSION: Presence of UTI in pregnancy, particularly in the third trimester, is strongly associated with PE. This association supports the hypothesis that the risk of PE is enhanced by an increased maternal inflammatory burden. Prophylaxis against UTI represents a potentially low-cost global intervention to slow or halt the development of PE.

Introduction

Preeclampsia (PE) is characterized by new-onset or worsening hypertension combined with proteinuria and associated signs and symptoms >20 weeks’ gestational age.1 Although overall mortality from PE has decreased in recent years, it represents a major cause of maternal morbidity and mortality, particularly in developing countries.2,3 In a large cohort of patients from low- and middle-income countries, PE conferred a 4-fold increase of maternal death and nearly a 2-fold increase in perinatal death, preterm birth, and low birthweight.4 Despite decades of research, and much progress in discernment of biomarkers in the maternal circulation, the pathogenesis of PE remains elusive.5

Redman and Sargent6 suggest that pregnancy itself is a state of excess systemic inflammation. In their conceptualization, PE becomes more likely when the level of systemic inflammatory burden inherent in pregnancy itself exceeds the maternal capacity to compensate for this additional stress. If this is the case, then it is possible to hypothesize that conditions, such as infectious disease, that increase systemic inflammatory burden should also increase the risk of PE. This suggestion is not without precedent as there are multiple examples of the association between maternal infection and an increased risk of PE in the medical literature.7 A variety of systemic maternal infections including HIV, malaria, Chlamydia trachomatis, and periodontal disease have been suggested to increase the risk of PE.7,9 Since urinary tract infection (UTI) represents one of the most common maternal infections during pregnancy, one would expect an association with PE.10 Prior work has documented this association.11-15 However many of these studies were limited by small cohort sizes and insufficient control for covariates.

The present study is a secondary analysis of a robust contemporary obstetrical cohort recruited to examine the ability of longitudinally sampled maternal angiogenic concentrations to predict PE.16 We hypothesize that the occurrence of UTI during a pregnancy is associated with the later occurrence of PE in that pregnancy. As PE is believed to
be associated with aberrations in systemic angiogenic levels (placental growth factor [PIGF] and soluble isoform of VEGF receptor [sFLT]), we further hypothesize that there will be significant interactions between maternal angiogenic protein levels and the occurrence of UTI.6,17,18

Materials and Methods

Study subjects

Participants were initially enrolled at 3 tertiary care academic centers: Brigham and Women's Hospital and Beth Israel Deaconess Medical Center in Boston, MA, and the Hospital of the University of Pennsylvania in Philadelphia, PA. Women >18 years of age presenting for prenatal care <15 weeks’ gestation were eligible for enrollment. The only initial cohort exclusion criterion was higher-order multiple gestations (triplets or greater). The protocol was approved by institutional review boards at each institution, and written informed consent was obtained from all participating women.

A total of 2607 gestations with delivery at ≥ 24 weeks’ gestation were enrolled at the 3 study sites from October 2007 through June 2009. All subjects were prospectively enrolled in the first trimester. Among the 3 sites, Brigham and Women’s Hospital contributed 48% of the participants with Beth Israel Deaconess Medical Center and Hospital of the University of Pennsylvania contributing 29% and 23%, respectively. This analysis further excluded women with a history of renal disorders (n = 18; 0.7%). Study visits occurred at the following median (interquartile range) weeks of gestation for all participants: 10.0 (4.4-16.7), 17.8 (12.6-22.7), 26.0 (19.6-30.9), and 35.3 (31.3-39.4).

Specimen collection and laboratory assays

Maternal blood and urine samples were obtained at the 4 visits during the pregnancy. Approximately 10 mL of blood was drawn in EDTA plasma tubes at each study visit, and the samples were kept at 4°C until processing for storage within 4 hours of venipuncture. The specimens were centrifuged for 20 minutes, aliquoted, and stored at −80°C. Samples were shipped in batches on dry ice to Abbott Diagnostics where they were stored at −80°C until analysis. PIGF and sFlt-1 were measured using prototype ARCHITECT immunoassays (Abbott Laboratories, Abbott Park, IL) as previously described.16

Clinical data and definitions

Information on the index pregnancy and neonate were abstracted from the medical record and supplemented with data collected specifically for the study. Maternal blood pressure and urinary protein dip were recorded at each study visit. Participants completed a brief questionnaire for background clinical and demographic information.

Gestational hypertension (was defined as blood pressures ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic at study visits 2-4 with negative urinary protein testing. PE was defined as gestational hypertension with positive urinary protein testing (>300 mg/24 h or protein/creatinine >0.20).

We abstracted information about UTIs and other complications of pregnancy and pregnancy outcomes based on a comprehensive review of the patient’s medical records. UTI was diagnosed by the patient’s providers at each institution. For purposes of this study, a patient was considered to have UTI if she had symptoms such as dysuria and frequency along with a positive urinalysis or urine culture prompting antibiotic treatment by the patient’s provider. Therefore culture data were not universally obtained. Urinalysis was considered positive if bacteria, leukocyte esterase, or blood was present, but not if the only positive finding was proteinuria. The diagnosis of UTI was made prior to the diagnosis of PE. Women with diagnosis of UTI after diagnosis of PE were considered as having no UTI for purposes of this analysis.

The specific management of disorders varied by institution, but all cases of hypertensive disease were deidentified and reviewed by a panel of the study principle investigators. A final diagnosis was only assigned with the approval of this panel. Based on these criteria, 229 (8.8%) pregnancies were identified as PE and 138 (5.3%) as having gestational hypertension. Among PE patients 37 (16.2%) were identified with early PE ≤ 34 weeks.

Statistical methods

We first examined the sociodemographic and clinical characteristics of the study population based on UTI diagnosis. Differences by UTI status were tested by using Wilcoxon rank sum or χ2 tests for quantitative and categorical variables, respectively. Logistic regression models were used to describe the relationship between UTI and either gestational hypertension or PE diagnosis. In adjusted models, covariates were included on the basis of biological plausibility or those previously shown to be associated with PE and UTI. The included covariates were maternal body mass index, race/ethnicity, parity, history of PE or diabetes, current diagnosis of chronic hypertension or gestational diabetes, use of assisted reproductive technology, and twin pregnancy. Additional sensitivity analyses were performed examining the relationship between PE and UTI in both nulliparous women and women with no history of PE. Women were then stratified by trimester of UTI diagnosis to further examine the relationship between timing of UTI diagnosis and PE.

Levels of sFlt-1 and PIGF were compared to examine the role of angiogenic factors upon the relationship between PE and UTI. Maternal plasma concentrations of angiogenic factors at a given gestational age range for a given hypertensive diagnosis were compared between women with or without UTI using Wilcoxon rank sum. To take into account the longitudinal nature of the relationship we used linear mixed effect models to generate random slopes and intercepts for either PIGF or s-FLT over time. These random intercepts and slopes were then used as predictors in the adjusted logistic regression models. Analysis was performed using SAS, Version 9.4 (SAS Institute Inc, Cary, NC) and R, Version 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The clinical and demographic characteristics of the cohort are presented in
Among 2589 patients enrolled in this cohort, UTI was significantly associated with the development of PE in the same pregnancy. The association was strongest among sFlt-1 profiles based on UTI status.

**Comment**

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for early PE severe enough to require delivery <34 weeks. The association was present albeit weaker among PE that occurred later or was mild enough to allow later delivery. The association was strongest when the UTI occurred in the third trimester. While angiogenic concentrations were not markedly different based on UTI status in cross-sectional analysis, longitudinal profiles of PLGF across pregnancy were significantly higher in women who developed UTI.

Our findings are supported by several prior works. Of the 17 studies reviewed in the metaanalysis by Conde-Agudelo et al, 12 studies found an association between UTI and PE with a pooled OR of 1.57 (95% CI, 1.45−1.7). Definitions of UTI in the reviewed studies varied and ranged between the report of urinary symptoms up to asymptomatic bacteriuria and pyelonephritis. A recent secondary analysis of a large World Health Organization cohort in low- and middle-income countries demonstrated an association between UTI and PE with an OR of 1.13 (95% CI, 1.03−1.24). Additionally, Minassian and colleagues reported a similar association between UTI and PE in a nested case-control study from the United Kingdom with an OR of 1.22 (95% CI, 1.03−1.45). Our study supports the connection between UTI and PE in a large, prospectively collected, contemporary obstetric cohort.

In addition to its large size and prospective nature, our study avoids many of the pitfalls of other works. Previous studies investigating the relationship between UTI and PE are limited by definition of UTI, the relative timing of the diagnoses, and the recognition of potential confounders. A major limitation in many studies in the literature, some of which were included in the recent metaanalysis, involve the timing of UTI diagnosis. Many studies failed to clarify the timing of UTI diagnosis relative to PE diagnosis or included patients who developed UTI after PE in their analysis. Of those studies that ensured PE developed after UTI, 5 failed to demonstrate a relationship between the 2 diseases. Antecedent diagnosis of UTI would be necessary for any study to ensure infection is on the causal pathway for PE and would ensure that women with PE are not being diagnosed with UTI due to more frequent visits with clinicians. The exclusion of patients with preexisting renal disease limited contributions from effect modification and the robust set of clinical variables allowed for controlling of multiple confounders and covariates. Furthermore, our study is the first to investigate molecular mechanisms in conjunction with UTI that may potentially be on the causal pathway. Although patients with PE are known to have aberrant values of the soluble angiogenic factors, there was no apparent association between UTI and the concentrations of the angiogenic factors in our study at individual study visits. Contrary to our findings, Chaivorapannga et al showed decreased plasma concentrations of PGF in patients with acute pyelonephritis in pregnancy and found that among PE patients, these concentrations were markedly decreased.

This connection between aberrant angiogenic factors in pregnant patients with infections has also been demonstrated in pregnant patients with

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All preeclampsia, N = 229</td>
<td>4.9 (3.3−7.4)</td>
<td>&lt;.0001</td>
<td>2.9 (1.8−4.6)</td>
<td>&lt;.0001</td>
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<tr>
<td>Preeclampsia ≤ 34 wk, N = 37</td>
<td>10.8 (5.2−22.5)</td>
<td>&lt;.0001</td>
<td>5.5 (2.3−12.7)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Preeclampsia &gt;34 wk, N = 197</td>
<td>4.0 (2.5−6.4)</td>
<td>&lt;.0001</td>
<td>2.5 (1.5−4.1)</td>
<td>.0006</td>
</tr>
<tr>
<td>Nulliparous participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All preeclampsia, N = 72</td>
<td>7.2 (3.6−14.2)</td>
<td>&lt;.0001</td>
<td>5.1 (2.4−10.6)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI occurrence in first trimester, N = 38</td>
<td>3.7 (1.7−7.9)</td>
<td>.0008</td>
<td>2.4 (1.0−5.6)</td>
<td>.04</td>
</tr>
<tr>
<td>UTI occurrence in second trimester, N = 33</td>
<td>3.2 (1.4−7.4)</td>
<td>.007</td>
<td>1.7 (0.7−4.3)</td>
<td>.26</td>
</tr>
<tr>
<td>UTI occurrence in third trimester, N = 55</td>
<td>7.3 (4.2−12.8)</td>
<td>&lt;.0001</td>
<td>4.3 (2.3−8.0)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio.

malaria, using the antiangiogenic protein soluble endoglin, which has been shown to be decreased in patients with PE.\textsuperscript{24} Case reports of placental infection leading to hydrops and PE have also demonstrated derangements in these antiangiogenic factors.\textsuperscript{25,26} Inflammatory cytokines play an important role in angiogenesis related to disease processes in inflammatory bowel disease and diabetic retinopathy highlighting the relationship between inflammation and neovascularization.\textsuperscript{27,28} Our study is the first to underscore the connection between angiogenic factors and the inflammatory pathophysiology of PE in this comprehensive longitudinal manner.

Alternatively, in our longitudinal analysis of angiogenic profiles and UTI status we observed a positive interaction with PlGF indicating that the occurrence of UTI is associated with increased concentrations of PlGF across pregnancy. Decreased rather than increased levels of PlGF are associated with PE.\textsuperscript{16} Taken together, we interpret the results of the interaction as suggesting that when PE occurs in association with UTI, it is mediated by intermediate effects other than the levels of the angiogenic proteins. Recent work has suggested that PE may have subtypes including those “angiogenic” and those that are not.\textsuperscript{29} In the contemporary cohort described by Rana et al,\textsuperscript{29} women with a normal sFlt-1 to PlGF ratio were more likely to have comorbid maternal medical conditions such as obesity and diabetes supporting a maternal phenotype of the disease. In addition to fewer co-morbid maternal conditions, women with elevated sFlt-1 to PlGF ratios had more severe presentations, were less likely to have comorbid maternal medical conditions such as obesity and diabetes, and were more likely to present at an earlier gestational age with more severe clinical features and adverse outcomes.\textsuperscript{29} Other authors have also suggested that PE may be a heterogeneous pathology with varying angiogenic factor levels and clinical presentations.\textsuperscript{30} These alternative classifications of the disease

| TABLE 5 |
| Longitudinal maternal angiogenic factor—adjusted odds ratios (95% confidence intervals) of preeclampsia in association with maternal urinary tract infection |

<table>
<thead>
<tr>
<th>UTI</th>
<th>Adjusted OR\textsuperscript{a} (95% CI)</th>
<th>(P\text{value})</th>
<th>Beta ((P\text{value}) interaction with sFLT)</th>
<th>Adjusted OR\textsuperscript{b} (95% CI)</th>
<th>(P\text{value})</th>
<th>Beta ((P\text{value}) interaction with PlGF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>3.0 (1.9–4.8)</td>
<td>&lt;.0001</td>
<td>−6.4 (0.82)</td>
<td>3.0 (1.9–4.7)</td>
<td>&lt;.0001</td>
<td>47.3 (0.01)</td>
</tr>
</tbody>
</table>

\(\text{CI}\), confidence interval; OR, odds ratio; UTI, urinary tract infection.

\textsuperscript{a} Model 1: adjusted for maternal body mass index, race, parity, personal history of preeclampsia, gestational diabetes, history of diabetes, chronic hypertension, use of assisted reproductive technology, twins, and sflt slope.

\textsuperscript{b} Model 2: Adjusted for maternal body mass index, race, parity, personal history of preeclampsia, gestational diabetes, history of diabetes, chronic hypertension, use of assisted reproductive technology, twins, and plgf slope.

\textsuperscript{c} Model 1: adjusted for maternal body mass index, race, parity, personal history of preeclampsia, gestational diabetes, history of diabetes, chronic hypertension, use of assisted reproductive technology, twins, and sflt slope.

\textsuperscript{d} Model 2: Adjusted for maternal body mass index, race, parity, personal history of preeclampsia, gestational diabetes, history of diabetes, chronic hypertension, use of assisted reproductive technology, twins, and plgf slope.

\textsuperscript{e} Model 1: adjusted for maternal body mass index, race, parity, personal history of preeclampsia, gestational diabetes, history of diabetes, chronic hypertension, use of assisted reproductive technology, twins, and sflt slope.

\textsuperscript{f} Model 2: Adjusted for maternal body mass index, race, parity, personal history of preeclampsia, gestational diabetes, history of diabetes, chronic hypertension, use of assisted reproductive technology, twins, and plgf slope.
fit nicely into the earlier theoretical work of Redman and Sargent when they attempted to classify PE as either of “placental” or “maternal” origins.

Our study had several strengths, including a repeated time point assessment of angiogenic factors, ultrasound dating of gestational age, physician-validated clinical outcomes, and a large number of subjects including both PE and UTI cases that allowed for exploring the timing effects of UTI diagnosis and odds of developing PE. The definition of UTI employed here is robust and conforms to typical clinical practice based on the judgment of the treating physician. In contemporary clinical context, UTI is most often diagnosed and treated based on symptoms and urinalysis rather than on culture-specific results. We acknowledge that additional work will be required to demonstrate a possible causal like between UTI and PE and further elucidate the role of inflammation using inflammatory biomarkers. If such a link could be demonstrated, then attention to the prevention of UTI early in pregnancy may represent an effective means to decrease the burden of PE, particularly in low-resource settings.

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4. Bilano VL, Ota E, Ganchimeg T, Mori R,インターネットs, which may lead to an in-...


Author and article information
From the Brigham and Women’s Hospital/Massachusetts General Hospital Integrated Residency Program in Obstetrics and Gynecology, Boston, MA (Dr Easter); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Brigham and Women’s Hospital, Boston, MA (Drs Cantonwine, Zera, and McElrath); Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, MA (Dr Lim); and Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Hospital of the University of Pennsylvania, Philadelphia, PA (Dr Parry).

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Corresponding author: Sarah Rae Easter, MD. sreaster@partners.org