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The Effect of Blood on the Protein to Creatine Ratio during Pregnancy

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Abstract

The protein-creatinine (PC) ratio is a laboratory value utilized frequently for the diagnosis of pre-eclampsia. Our study looks at the effects of blood on the PC ratio. Urine can be contaminated with blood for multiple etiologies common in pregnancy. We collected urine and blood samples from pregnant patients of at least 20 weeks' gestation. Patients were screened to exclude baseline proteinuria, defined as a prior PC ratio < 0.3 within 24 hours prior to enrollment. The threshold of 0.3 mg/mg is based on prior validation studies demonstrating correlation with ≥300 mg of protein in a 24-hour urine collection. A urinalysis and PC ratio were completed on samples. Our study found that urine contaminated with blood, ranging from microscopic to visible hematuria, will falsely elevate the PC ratio. Straight catheterization may be required for diagnosing preeclampsia in an obstetric patient when there is concern for blood contamination. These findings support cautious interpretation of PC ratios in visibly bloody specimens and consideration of repeat sampling when contamination is suspected.

Keywords

Preeclampsia, Protein-Creatinine Ratio, Proteinuria, Hematuria

1. Introduction

The urine protein-to-creatinine (PC) ratio is commonly used as a rapid alternative to 24-hour urine collection for diagnosing proteinuria and preeclampsia after 20 weeks of gestation [1]. The commonly accepted diagnostic threshold of 0.3 mg/mg originates from studies correlating spot urine protein-creatinine ratios with 24-hour urine protein excretion. Early work demonstrated that a ratio of approxi-

mately 0.3 corresponds to 300 mg of protein over 24 hours, which is the traditional cutoff for clinically significant proteinuria [2] [3]. Subsequent studies in pregnant populations validated this cutoff, showing reasonable sensitivity and specificity for detecting ≥300 mg/day proteinuria [4] [5]. This threshold has been adopted in clinical practice guidelines, including those from the American College of Obstetricians and Gynecologists [6].

An accurate PC ratio is of paramount importance for the clinical management of pregnant patients, especially when diagnosing preeclampsia and the hypertensive disorders of pregnancy. However, hematuria has been shown in animal models to artificially elevate the PC ratio [7]. We hypothesized that contamination of urine with blood would falsely increase the PC ratio in pregnant patients.

2. Materials and Methods

We conducted a prospective study of 20 pregnant patients ≥ 20 weeks' gestation presenting to labor and delivery triage or antepartum unit with hypertension (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg). Inclusion criteria included singleton pregnancy, age ≥ 18 years, and absence of baseline proteinuria as defined by PC ratio < 0.3. Exclusion criteria included urinary tract infection, active vaginal bleeding, known hematuria, or preexisting proteinuria. After informed consent, each patient provided an 80 mL urine sample and venous blood.

For the first 10 samples, urine was divided into 20 mL aliquots. Whole blood was added in increasing volumes, 0 mL, 1 mL, 2 mL, and 5 mL (**Figure 1**). Urinalysis and PC ratio were performed on each specimen. The subsequent 10 samples, urine was again divided into 20 mL aliquots. This time, blood was added at volumes of 0 μL, 1 μL, 2 μL, and 3 μL.

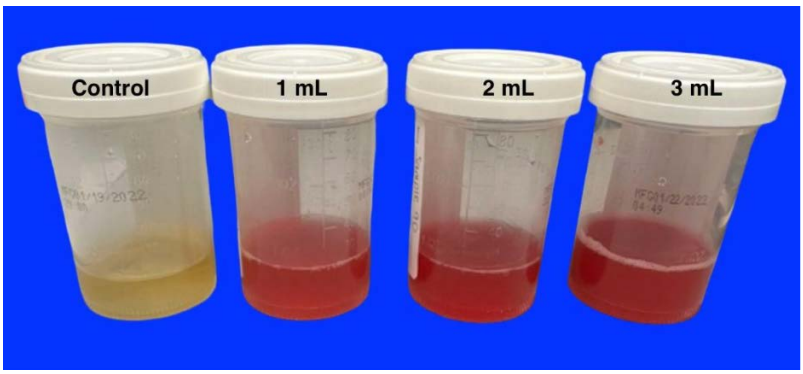

Figure 1. Control with visible change in color after adding 1 mL, 2 mL, and 5 mL of whole blood.

The use of two blood addition schemes was intentional to model clinically relevant contamination ranges: millimeter-scale volumes to stimulate gross hematuria and microliter-scale volumes to simulate microscopic hematuria.

Results were entered into a database and analyzed using statistical software, SAS 9.4 (SAS Institute, Cary, NC, USA). A linear mixed-effects model was used with

PC ratio as the dependent variable, blood volume as a fixed effect, and subject as a random intercept to account for repeated measures within each urine sample. A compound symmetry covariance structure was assumed. Pairwise comparisons were adjusted using the Tukey method for multiple testing. In addition, multivariate analysis of variance (MANOVA) was performed to evaluate the overall effect of blood contamination on multiple urinalysis parameters simultaneously. The study was approved by the Institutional Review Board at Marshall University (1912480-1).

3. Results

The mean baseline for controls was a PC ratio of 0.25. Adding 1 mL, 2 mL, and 5 mL of whole blood caused an increase in mean PC ratios to 3.41, 6.75, and 14.85, respectively. Only with the addition of 3 μL was the PC ratio increased significantly (Table 1).

Table 1. Group comparisons.

Amount Added Comparison		Estimates	p-value
Dose 1	Dose 2		
1 μL	2 μL	−0.00073	0.9307
1 μL	3 μL	−0.01682	0.0514
1 μL	0	0.008545	0.3108
2 μL	3 μL	−0.01609	0.0617
2 μL	0	0.009273	0.2722
3 μL	0	0.02536	0.0046

As these PC ratios exceeded the preeclampsia diagnostic threshold of 0.3 mg/dL, further investigation into the impact of microhematuria was performed. The mean baseline for controls for the new dilution was a PC ratio of 0.11. Adding 1 μL, 2 μL, and 3 μL caused an increase in mean PC ratios to 0.123, 0.124, and 0.145, respectively. The PC ratio increased with greater amounts of blood added to each sample. Only with the addition of 3 μl was the PC ratio increased significantly. The effect was particularly evident when comparing larger differences in blood volume, such as 1 μL versus 3 μL and 0 μL versus 3 μL, both of which produced statistically significant increases in PC ratio (Table 1). In contrast, smaller dilution differences did not yield significant changes. Notably, once 3 μL of whole blood was added, the urine color was not visibly altered from baseline. These findings suggest that gross hematuria can falsely elevate PC ratios, whereas microscopic blood contamination has minimal impact.

4. Discussion

The use of the PC ratio test in obstetrics is recommended as a diagnostic tool to

determine the degree of proteinuria, specifically in the diagnosis of preeclampsia. While a 24-hour urine collection for protein can accurately measure any fluctuation of proteinuria that may occur throughout the collection period, studies have confirmed the validity of the utilization of the PC ratio as an alternative [8]. There have been no studies in humans to validate the PC ratio as a diagnostic tool in the setting of hematuria, even though urine samples are often contaminated with blood in the obstetric population.

Our findings demonstrate that gross blood contamination significantly and falsely elevates the PC ratio beyond the diagnostic threshold for preeclampsia. In contrast, microscopic levels of blood contamination produced statistically detectable increases but remained below the diagnostic threshold in this cohort.

These results suggest that visibly blood-contaminated urine specimens may lead to false-positive interpretations, whereas microscopic contamination is less likely to result in clinically significant misclassification.

From a clinical standpoint, if a urine sample appears visibly bloody and an accurate assessment of proteinuria is required, obtaining a repeat specimen (e.g. via straight catheterization) should be considered to improve diagnostic accuracy. This recommendation reflects a clinical implication rather than an intervention directly tested in this study.

Limitations

This study has severe limitations. First, the ex vivo design using blood-spiked urine may not fully replicate *in vivo* hematuria. Secondly, the study was conducted at a single center with a small sample size, limiting generalizability. Larger, multicenter studies with *in vivo* validation are needed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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