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Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review

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ABSTRACT

Objective To review the spot protein:creatinine ratio and albumin:creatinine ratio as diagnostic tests for significant proteinuria in hypertensive pregnant women.

Design Systematic review.

Data sources Medline and Embase, the Cochrane Library, reference lists, and experts.

Review methods Literature search (1980-2007) for articles of the spot protein:creatinine ratio or albumin:creatinine ratio in hypertensive pregnancy, with 24 hour proteinuria as the comparator.

Results 13 studies concerned the spot protein:creatinine ratio (1214 women with primarily gestational hypertension). Nine studies reported sensitivity and specificity for eight cut-off points, median 24 mg/mmol (range 17-57 mg/mmol; 0.15-0.50 mg/mg). Laboratory assays were not well described. Diagnostic test characteristics were recalculated for a cut-off point of 30 mg/mmol. No significant heterogeneity in cut-off points was found between studies over a range of proteinuria. Pooled values gave a sensitivity of 83.6% (95% confidence interval 77.5% to 89.7%), specificity of 76.3% (72.6% to 80.0%), positive likelihood ratio of 3.53 (2.83 to 4.49), and negative likelihood ratio of 0.21 (0.13 to 0.31) (nine studies, 1003 women). Two studies of the spot albumin:creatinine ratio (225 women) found optimal cut-off points of 2 mg/mmol for proteinuria of 0.3 g/day or more and 27 mg/mmol for albuminuria.

Conclusion The spot protein:creatinine ratio is a reasonable "rule-out" test for detecting proteinuria of 0.3 g/day or more in hypertensive pregnancy. Information on use of the spot albumin:creatinine ratio in these women is insufficient.

INTRODUCTION

Urine collection over 24 hours is considered the traditional comparator for quantification of proteinuria

in pregnancy,¹⁻⁴ but it has limitations: the urine requires refrigeration; collection is cumbersome, time consuming, and potentially misleading if done inaccurately; and collection may not be possible during delivery. Timed collections also delay diagnosis and may result in prolonged hospital stay for investigations.

Alternatives for the diagnosis of proteinuria in pregnancy have been considered. These include urinary dipsticks, urine collections over a shorter period, the urinary spot protein:creatinine ratio, and the urinary spot albumin:creatinine ratio. Australasian and international guidelines advocate use of the urinary spot protein:creatinine ratio as an alternative to 24 hour urine collection.^{3,4}

We carried out a systematic review to assess the accuracy of the spot protein:creatinine ratio and spot albumin:creatinine ratio compared with 24 hour urinary collection for the detection of significant proteinuria in hypertensive pregnant women.

METHODS

We did a search (see bmj.com) of diagnostic studies that compared the urinary spot protein:creatinine ratio or albumin:creatinine ratio with urinary protein excretion over 24 hours among hypertensive pregnant women.

We assessed study quality using the quality assessment of studies of diagnostic accuracy in a systematic reviews tool.⁵

Information was recorded on characteristics of the study and participants, how the diagnostic tests were carried out and the results, and methods for assessing the diagnostic accuracy of the tests. When positive and negative likelihood ratios were missing we calculated them from sensitivity and specificity (see bmj.com).

For each study we analysed sensitivity, specificity, likelihood ratios, and area under the receiver operating curves, according to reported cut-off points (we used a conversion factor of 1.13 to transform results for the spot

protein:creatinine ratio from mg protein/mg creatinine to mg/mmol). To explore whether diagnostic accuracy differed significantly between studies we chose a cut-off point of 30 mg protein/mmol creatinine.³ From provided data we used contingency tables to recalculate sensitivity, specificity, and likelihood ratios for as near a cut-off point of 30 mg/mmol as possible. When the prevalence of significant proteinuria was unavailable we used the median prevalence from the studies to generate contingency tables.

To allow for variation in diagnostic threshold we assessed statistical heterogeneity between studies using the Littenberg and Moses regression method.⁶ In the absence of heterogeneity we calculated new measures of diagnostic accuracy using data from each study (see *bmj.com*). We carried out sensitivity analyses by excluding studies when they differed methodologically from most or all others.

RESULTS

The search yielded 1416 citations (see *bmj.com*). One publication was not in English or French and was excluded.⁷ Thirteen studies were published on the spot protein:creatinine ratio (1214 women)^{w1-13} and two on the spot albumin:creatinine ratio (225 women).^{w14 w15}

Spot protein:creatinine ratio

Validity assessment

The study quality score ranged from 7 to 12 (see *bmj.com*).⁵ Most of the studies were prospective (n=10) and cross sectional (n=11). None mentioned how many women of those eligible were enrolled, and only two stated recruitment of consecutive, eligible women.^{w3 w13} Ten studies stated reasons for withdrawals or exclusions.^{w1 w2 w5-w7 w9-w13} Incomplete pairs of tests ranged from 11-32% of samples.^{w1 w4 w10 w12 w13} Reasons for incomplete collections included inadequate collection procedures and delivery.

Characteristics of studies and participants

Studies of the spot protein:creatinine ratio analysed samples from 30-220 women (median 75). The women had gestational hypertension (five studies), gestational hypertension with proteinuria of + or more (n=5), or any hypertensive disorder of pregnancy (n=3). Ten studies enrolled inpatients. Two studies excluded women who needed bed rest.^{w11 w13} Six studies excluded women with underlying medical disease^{w1 w2 w5 w7 w9 w12} and six excluded women with urinary tract infection or bacteriuria.^{w1 w6 w7 w9 w11 w12}

Diagnostic tests

The prevalence of significant proteinuria varied from 21-83% (median 55%, n=11; see *bmj.com*). The range of 24 hour proteinuria varied from 0-26.5 g/day (n=11) and that for the spot protein:creatinine ratio varied from 0-2991 mg/mmol (n=9).

The timing of the spot protein:creatinine ratio relative to 24 hour urine collection varied: before (n=9), after (n=1), before or after (n=1), or during (n=2). Nine studies stated that the spot protein:creatinine ratio was not based on the first voided sample of the day.^{w1 w3 w6-w9 w11-w13} In four studies, completeness of the 24 hour urine collection was assessed by urinary creatinine excretion^{w1 w5 w10 w11} or questioning the women.^{w13} In one study, urine was

collected by Foley catheter.^{w2}

Urinary protein and creatinine were measured by many different laboratory methods. At least five analytical methods were used for protein^{w1-w13} and at least two were used for creatinine.^{w1 w5-w7 w13}

Diagnostic test results

Two studies reported only correlation coefficients.^{w3 w4} The area under the curve was reported by nine of the 11 remaining studies (range 0.82-0.97).^{w1 w2 w7-w13} A cut-off point for the spot protein:creatinine ratio that maximised both sensitivity and specificity could be identified for nine of the 11 studies. The reporting of cut-off points varied and units differed widely. Eight cut-off points were used, with a median of 24 mg/mmol and range 17-57 mg/mmol (0.15-0.5 mg/mg). The median sensitivity was 91% (range 73-97%) and median specificity 90% (range 41-100%). The median positive likelihood ratio was 9.1 (range 1.54 to infinity) and median negative likelihood ratio was 0.14 (range 0.04-0.37). One study presented a Bland-Altman plot to assess agreement between the spot protein:creatinine ratio and 24 hour proteinuria and found good agreement.^{w8}

Quantitative data synthesis

Nine studies had data necessary to determine a cut-off point of 30 mg/mmol (see *bmj.com*).^{w1 w2 w5 w7-w9 w11-w13} Sensitivity and specificity did not seem to be related to the prevalence of significant proteinuria, or the range of proteinuria (see *bmj.com*). No significant heterogeneity was shown between studies for the new measures of diagnostic accuracy for the cut-off point of 30 mg/mmol (P=0.94); in these calculations, 0.99 was used when reported specificity was 1.00.^{w9}

Summary measures of diagnostic accuracy were: sensitivity 83.6% (95% confidence interval 77.5% to 89.7%), specificity 76.3% (72.6% to 80.0%), positive likelihood ratio 3.53 (2.83 to 4.49), and negative likelihood ratio 0.21 (0.13 to 0.31) (1003 women). When the prevalence of significant proteinuria was varied from 0.25 to 0.75 for one study without known prevalence the pooled sensitivities and specificities did not differ.^{w8} Exclusion of one study^{w2} that used a catheter resulted in a pooled sensitivity of 84.8% (78.7% to 90.8%) and pooled specificity of 79.1% (75.3% to 82.8%) (809 women).

Spot albumin:creatinine ratio

The two studies of the spot albumin:creatinine ratio were of good quality.⁵ Overall, 225 women were referred with gestational hypertension^{w15} or any pregnancy hypertension.^{w14} Seventy seven (45%) women had proteinuria of 0.3 g/day or more.^{w15} The 24 hour urinary albumin excretion ranged from 0-11.2 g/day and spot albumin:creatinine ratio from 0.3-640 mg/mmol.^{w14} Diagnostic accuracy for the spot albumin:creatinine ratio was excellent compared with 24 hour proteinuria (cut-off point 2 mg/mmol, sensitivity 94%, specificity 94%, positive likelihood ratio 15.7, negative likelihood ratio 0.06)^{w15} or with 24 hour albuminuria (cut-off point 27 mg/mmol, sensitivity 95%, specificity 100%, positive likelihood ratio infinity, negative likelihood ratio 0.05).^{w14} It was not possible to pool the results for the spot albumin:creatinine ratio because of the different standards used for comparison.

DISCUSSION

The quantification of proteinuria is central to the investigation of hypertensive pregnant women. Relevant Australasian and international guidelines advocate use of the spot protein:creatinine ratio.³⁴ The test is available from any laboratory that determines protein and creatinine concentrations in 24 hour urine collections.

We identified 13 studies (1214 women) of the spot protein:creatinine ratio used in hypertensive pregnant women. Eight cut-off points were published, which seemed to differ, in part because of the variability in the units used for urinary protein and urinary creatinine. This was further complicated by the different populations of pregnant women. We included studies that focused only on women with a hypertensive disorder of pregnancy, in whom we believe the spot protein:creatinine ratio has the greatest potential use.

The sensitivities and specificities in the studies of the spot protein:creatinine ratio varied, as expected, by chance alone. We compared diagnostic accuracy results using a cut-off point of 30 mg/mmol for the spot protein:creatinine ratio, as recommended.³⁴ The pooled results were not sensitive to the range of proteinuria or method of urine collection. Overall, the positive likelihood ratio was poor to fair. The negative likelihood ratio, however, was fair to good, suggesting that a spot protein:creatinine ratio of less than 30 mg/mmol is a reasonable “rule-out” test for proteinuria of 0.3 g/day or more.

We identified two studies (225 women) that examined use of the spot albumin:creatinine ratio in pregnancy. The test was excellent at diagnosing proteinuria or albuminuria of 0.3 g/day or more but data are too limited to advocate use of the test in pregnancy.

The strengths of our review include our focus on hypertensive pregnant women and pregnant women admitted to hospital (inpatients or outpatients). These women had a wide range of proteinuria and a spectrum of hypertension seen in clinical practice. We reported favourable diagnostic test characteristics for a recommended cut-off point of 30 mg/mmol.³⁴

Our review has limitations. We excluded abstracts and one article published in a language other than English or French. The included studies focused on inpatients. Reporting of completeness of 24 hour urine collection was inadequate. Laboratory assays for protein, albumin, and creatinine varied. Study quality was not uniformly high. Despite these limitations we found no significant heterogeneity between studies in diagnostic accuracy of the spot protein:creatinine ratio.

Perhaps the most important limitation of the literature on which this review is based was using the 24 hour urine collection as the standard against which all other tests of proteinuria were compared. The 24 hour urine collection has well documented problems with completeness, timeliness, and ease of performance. In pregnancy, problems are increased by the dilation of the ureters and incomplete bladder emptying.⁸ Errors can be avoided by adequate hydration to maintain urine flow and standardisation of the technique at the beginning and end of the collection.

It follows from these limitations in pregnancy that the 24 hour urine collection should not be the standard against which new measures are evaluated. The error to which the

spot urine sample is susceptible—potential mild diurnal variations in protein excretion—is likely to be outweighed by the error associated with 24 hour urine collection.

The spot protein:creatinine ratio seems to be a reasonable “rule-out” test for proteinuria of 0.3 g/day or more among otherwise healthy hypertensive pregnant women with or without proteinuria on dipstick. Of the 13 included studies in our review, nine did not use the first voided urine sample for the spot protein:creatinine ratio, suggesting that the test is useful throughout the day.

The spot protein:creatinine ratio is convenient and timely when laboratories carry out daily analysis of protein and creatinine. As such, women may be able to avoid admission to hospital and be reassessed easily if needed. Proteinuria is only one diagnostic criterion for pre-eclampsia, and complications can occur in the absence of proteinuria.

We do not advocate use of the spot protein:creatinine ratio or spot albumin:creatinine ratio for monitoring or quantifying proteinuria in pregnancy. Only at extremes have higher compared with lower levels of proteinuria been associated with higher maternal or perinatal mortality or morbidity,⁹⁻¹³ and quantification of proteinuria has not predicted short term maternal renal failure or ongoing proteinuria post partum.¹²⁻¹⁵ The spot protein:creatinine ratio has not been reliable for quantifying proteinuria during pregnancy.^{16,17}

Since the late 1990s many studies have favourably compared the spot urinary protein:creatinine ratio with 24 hour proteinuria, but the test has not been widely adopted in obstetric practice. Reasons for this need exploring.

A need exists for information about the validity of the spot protein:creatinine cut-off point of 30 mg/mmol for detection of adverse pregnancy outcomes among both inpatients and outpatients with suspected pre-eclampsia.

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Ethical approval: not required for this diagnostic meta-analysis of published studies.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies have found that the spot protein:creatinine ratio compares favourably with 24 hour urinary protein estimation, the traditional comparator for measuring proteinuria in pregnancy. Many cut-off points for detection of proteinuria of 0.3 g/day or more have been published.

WHAT THIS STUDY ADDS

The 24 hour urine collection should not be the standard against which new measures of proteinuria or albuminuria are compared in pregnancy.

The spot urinary protein:creatinine ratio is a reasonable "rule-out" test for significant proteinuria of 0.3 g/day or more in pregnancy.

Information about the spot urinary albumin:creatinine ratio is insufficient to suggest a cut-off point for diagnosis of significant proteinuria in pregnancy.

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Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis

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ABSTRACT

Objective To systematically review the efficacy of steroids in the prevention of acute respiratory distress syndrome (ARDS) in critically ill adults, and in treatment for established ARDS.

Data sources Search of randomised controlled trials (1966-April 2007) of PubMed, Cochrane central register of controlled trials, Cochrane database of systematic reviews, American College of Physicians Journal Club, health technology assessment database, and database of abstracts of reviews of effects.

Data extraction Two investigators independently assessed trials for inclusion and extracted data into standardised forms; differences were resolved by consensus.

Data synthesis Steroid efficacy was assessed through a Bayesian hierarchical model for comparing the odds of developing ARDS and mortality (both expressed as odds ratio with 95% credible interval) and duration of ventilator free days, assessed as mean difference. Bayesian outcome probabilities were calculated as the probability that the odds ratio would be ≥ 1 or the probability that the mean difference would be ≥ 0 . Nine randomised trials using variable dose and duration of steroids were identified. Preventive steroids (four studies) were associated with a trend to increase both the odds of patients developing ARDS (odds ratio 1.55, 95% credible interval 0.58 to 4.05; P(odds

ratio ≥ 1)=86.6%), and the risk of mortality in those who subsequently developed ARDS (three studies, odds ratio 1.52, 95% credible interval 0.30 to 5.94; P(odds ratio ≥ 1)=72.8%). Steroid administration after onset of ARDS (five studies) was associated with a trend towards reduction in mortality (odds ratio 0.62, 95% credible interval 0.23 to 1.26; P(odds ratio ≥ 1)=6.8%). Steroid therapy increased the number of ventilator free days compared with controls (three studies, mean difference 4.05 days, 95% credible interval 0.22 to 8.71; P(mean difference ≥ 0)=97.9%). Steroids were not associated with increase in risk of infection.

Conclusions A definitive role of corticosteroids in the treatment of ARDS in adults is not established. A possibility of reduced mortality and increased ventilator free days with steroids started after the onset of ARDS was suggested. Preventive steroids possibly increase the incidence of ARDS in critically ill adults.

INTRODUCTION

It would seem logical to use corticosteroids to treat acute respiratory distress syndrome (ARDS), with its protracted inflammation. Clinical outcomes in trials on the role of steroids in ARDS^{w1-w5} have varied, however, and two recent overviews on the efficacy of steroids in ARDS reached opposite conclusions.^{1,2} We assessed whether steroids are associated with mortality benefit in adults with ARDS. We also determined the effect of