Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis

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CRD summary
The authors concluded that protein to creatinine ratio had promising diagnostic value for significant proteinuria in women with suspected pre-eclampsia, but its use in clinical practice was unclear. There was insufficient evidence on albumin to creatinine ratio, and evidence on adverse pregnancy outcomes. Despite some limitations in the review, these tentative conclusions reflect the evidence presented and seem appropriate.

Authors' objectives
To determine the diagnostic accuracy of two spot urinary tests for detecting significant proteinuria or predicting adverse pregnancy outcome in patients with suspected pre-eclampsia.

Searching
Eight databases including MEDLINE, The Cochrane Library and DARE were searched between 1980 and January 2011; the search strategy was available online. No language restrictions were applied. Reference lists of eligible studies, relevant reviews and relevant journals (not specified) were manually searched for additional studies. Experts in the field were contacted.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs), diagnostic accuracy studies and observational studies that included at least ten pregnant women with suspected pre-eclampsia (hypertension with or without proteinuria). Eligible studies had to compare the diagnostic accuracy of random urinary protein to creatinine ratio or albumin to creatinine ratio (index tests) versus 24 hour urinary protein excretion (reference test) or adverse pregnancy outcomes to predict significant proteinuria (significant above 300 mg/24 hours, severe above 5000 mg/24 hours) or adverse outcomes in mothers or babies (as defined in original articles).

Included studies were conducted in secondary or tertiary care settings in various countries, such as the USA, Turkey, India and South Africa. Where reported, mothers’ age ranged from 15 to 49 years. Four studies were of women with hypertension and proteinuria confirmed by dipstick analysis. Some studies excluded patients with proven urinary tract infections, chronic hypertension or chronic renal disease. Four studies were of in-patients on bed rest. Measurement of protein and creatinine varied across studies; some studies excluded patients with inadequate urine collections. Prevalence of significant proteinuria ranged between 14% and 87%.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
At least one reviewer assessed study quality using the QUADAS and STARD tools.

Data extraction
Two reviewers independently extracted data into a 2x2 table to estimate sensitivity, specificity and positive and negative likelihood ratios. Associated standard errors were also extracted and 95% confidence intervals calculated.

Estimates were calculated for each protein to creatinine ratio or albumin to creatinine ratio threshold (range 0.13 to 0.49). Where studies did not report results for specific thresholds, these were calculated using estimated correlations from other included studies. Where cells contained zero events, 0.5 was added to each cell.

Discrepancies were resolved by consensus or referral to a third reviewer.

Methods of synthesis
Where meta-analysis was appropriate, a random-effects model was used to pool sensitivity, specificity, positive and negative likelihood ratios and their associated 95% confidence intervals (CIs). Pooling was performed for each protein to creatinine ratio or albumin to creatinine ratio threshold. Summary receiver operating characteristic curves were plotted using a multivariate approach that extended the Reitsma et al. approach and the area under the summary curve was calculated.

Subgroup analysis was undertaken in studies that included only women with confirmed hypertension and proteinuria on dipstick analysis. One study was excluded from the multivariate meta-analysis as it had unusual results.

Where pooling was not appropriate, individual study results were reported.

**Results of the review**

Twenty studies (2,978 participants analysed; range 15 to 927) were included in the review. Thirteen were cohort studies, four were cross sectional studies, one a case-control and two were diagnostic accuracy studies. Ten studies used prospective design (four of which recruited patients consecutively), one was a retrospective study and the design was unclear in nine studies. Only three studies reported blinding of assessors. Verification bias was minimised in 18 studies. Five studies had greater than 20% drop-out rates.

**Protein to creatinine ratio versus 24 hour urine collection (15 studies):** None of the studies assessed adverse pregnancy outcomes. Sensitivity estimates for the detection of proteinuria ranged from 0.65 to 0.89 depending on the threshold assessed; sensitivity decreased as thresholds increased. Specificity ranged from 0.63 to 0.87; specificity increased as thresholds increased. Positive likelihood ratios ranged from 2.38 to 4.90 and negative likelihood ratios ranged from 0.17 to 0.40. The area under the curve was 0.69 which suggested that the protein to creatinine ratio performed well in detecting proteinuria. The optimum threshold (maximises sensitivity and specificity jointly) appeared to be between 0.30 and 0.35 inclusive. There was evidence of significant heterogeneity across thresholds for which two or more studies were pooled. Other findings were reported in the review.

**Albumin to creatinine ratios versus 24 hour urine collection (five studies):** Four studies assessed accuracy of albumin to creatinine ratio for detecting proteinuria, but results could not be pooled due to different study characteristics and thresholds assessed. One study reported adverse pregnancy outcome results.

**Authors' conclusions**

Protein to creatinine ratio had promising diagnostic value for significant proteinuria in women with suspected pre-eclampsia. But there was insufficient evidence to determine how it should be used in clinical practice. There was insufficient evidence on the diagnostic use of albumin to creatinine ratio and the use of either test to predict adverse pregnancy outcomes.

**CRD commentary**

The review question was clear. A satisfactory literature search appeared to have been undertaken with attempts to minimise the potential for missed data. Data extraction was undertaken in duplicate, but other stages of the review process were not, so reviewer error and bias could not be ruled out. Study quality was assessed and there was potential for some risk of bias. Both qualitative and quantitative syntheses were undertaken, which seemed appropriate. Methods of quantitative synthesis seemed appropriate. Results for most protein to creatinine ratio thresholds were based on three studies or less. This reduced the robustness of the results. There were some limitations in the review process, but the conclusions reflect the evidence presented and the authors' tentative conclusions seem appropriate.

**Implications of the review for practice and research**

**Practice:** The authors stated that although the protein to creatinine ratio showed promising diagnostic value, how it should be implemented in clinical practice was unclear due to comparison with 24 hour urine collection only and wide variation across studies even at the same protein to creatinine ratio threshold. Clinicians should know the prevalence of significant proteinuria in the population and setting under investigation to allow accurate interpretation of the findings.

**Research:** The authors stated that further well-conducted research was needed to identify the causes of heterogeneity in test accuracy and identify situations where protein to creatinine ratio performs consistently well. The cost effectiveness of protein to creatinine ratio needed to be investigated.
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